

Priorities 4/8/97

(FILE 'USPAT' ENTERED AT 16:05:05 ON 05 OCT 1999)

E CLARY, DOUGLAS/IN

L1 1 S E4  
L2 92 S PROTEIN TYROSINE KINASE RECEPTOR# OR RECEPTOR PROTEIN TY  
ROS  
L3 3 S L2 AND RET  
L4 1934 S L1 AND EPIDERMAL GROWTH FACTOR RECEPTOR# OR RET  
L5 1 S L1 AND (EPIDERMAL GROWTH FACTOR RECEPTOR# OR RET)  
L6 3 S L3 AND (EPIDERMAL GROWTH FACTOR RECEPTOR# OR RET)  
L7 0 S L3 AND (C-RET OR C RET)  
L8 24 S C-RET OR C RET  
L9 10 S L8 AND RECEPTOR#  
L10 0 S ORPHAN C-RET OR ORPHAN C RET

FILE 'USPAT' ENTERED AT 16:05:05 ON 05 OCT 1999

=> e clary, douglas/in

E# FILE FREQUENCY TERM

E1 USPAT 2 CLARY, DERWIN R/IN  
E2 USPAT 1 CLARY, DONALD P/IN  
E3 USPAT 0 -> CLARY, DOUGLAS/IN  
E4 USPAT 1 CLARY, DOUGLAS O/IN  
E5 USPAT 1 CLARY, EDWARD L/IN  
E6 USPAT 1 CLARY, EVERETT/IN  
E7 USPAT 1 CLARY, EVERETT J/IN  
E8 USPAT 1 CLARY, HARRY E/IN  
E9 USPAT 1 CLARY, HARRY EARL/IN  
E10 USPAT 1 CLARY, HENRY JAMES/IN  
E11 USPAT 1 CLARY, HUGH L/IN  
E12 USPAT 2 CLARY, JAMES BARNEY/IN

=> se4

'SE4' IS NOT A RECOGNIZED COMMAND

=> s e4

L1 I "CLARY, DOUGLAS O"/IN

=> d ll

1. 5,753,225, May 19, 1998, Antibodies that mimic actions of neurotrophins; \*\*Douglas O. Clary\*\*, et al., 424/130.1, 141.1, 143.1, 156.1; 530/387.1, 388.1, 388.22 [IMAGE AVAILABLE]

=> s protein tyrosine kinase receptor# or receptor protein tyrosine kinase#

74984 PROTEIN  
14772 TYROSINE  
10785 KINASE  
40504 RECEPTOR#  
16 PROTEIN TYROSINE KINASE RECEPTOR#

(PROTEIN(W)TYROSINE(W)KINASE(W)RECEPTOR#)  
34275 RECEPTOR  
74984 PROTEIN  
14772 TYROSINE  
11325 KINASE#  
81 RECEPTOR PROTEIN TYROSINE KINASE#

(RECEPTOR(W)PROTEIN(W)TYROSINE(W)KINASE#)  
L2 92 PROTEIN TYROSINE KINASE RECEPTOR# OR  
RECEPTOR PROTEIN TYROS  
INE

KINASE#

=> s l2 and ret

1933 RET

L3 3 L2 AND RET

=> s ll and epidermal growth factor receptor# or ret

6446 EPIDERMAL  
156026 GROWTH  
276846 FACTOR  
40504 RECEPTOR#  
455 EPIDERMAL GROWTH FACTOR RECEPTOR#

(EPIDERMAL(W)GROWTH(W)FACTOR(W)RECEPTOR#)  
1933 RET

L4 1934 L1 AND EPIDERMAL GROWTH FACTOR  
RECEPTOR# OR RET

=> s ll and (epidermal growth factor receptor# or ret)

6446 EPIDERMAL  
156026 GROWTH  
276846 FACTOR  
40504 RECEPTOR#  
455 EPIDERMAL GROWTH FACTOR RECEPTOR#

(EPIDERMAL(W)GROWTH(W)FACTOR(W)RECEPTOR#)  
1933 RET

L5 1 L1 AND (EPIDERMAL GROWTH FACTOR  
RECEPTOR# OR RET)

=> s l3 and (epidermal growth factor receptor# or ret)

6446 EPIDERMAL  
156026 GROWTH  
276846 FACTOR  
40504 RECEPTOR#  
455 EPIDERMAL GROWTH FACTOR RECEPTOR#

(EPIDERMAL(W)GROWTH(W)FACTOR(W)RECEPTOR#)

1933 RET

L6 3 L3 AND (EPIDERMAL GROWTH FACTOR  
RECEPTOR# OR RET)

=> s l3 and (c-ret or c ret)

1373455 C  
1933 RET  
24 C-RET  
(C(W)RET)  
1373455 C  
1933 RET  
24 C RET  
(C(W)RET)  
L7 0 L3 AND (C-RET OR C RET)

=> s c-ret or c ret

1373455 C  
1933 RET  
24 C-RET  
(C(W)RET)  
1373455 C  
1933 RET  
24 C RET  
(C(W)RET)  
L8 24 C-RET OR C RET

=> d his

(FILE 'USPAT' ENTERED AT 16:05:05 ON 05 OCT 1999)

E CLARY, DOUGLAS/IN

L1 1 S E4  
L2 92 S PROTEIN TYROSINE KINASE RECEPTOR#  
OR RECEPTOR PROTEIN TY  
ROS  
L3 3 S L2 AND RET  
L4 1934 S L1 AND EPIDERMAL GROWTH FACTOR  
RECEPTOR# OR RET  
L5 1 S L1 AND (EPIDERMAL GROWTH FACTOR  
RECEPTOR# OR RET)  
L6 3 S L3 AND (EPIDERMAL GROWTH FACTOR  
RECEPTOR# OR RET)  
L7 0 S L3 AND (C-RET OR C RET)  
L8 24 S C-RET OR C RET

=> s l8 and receptor#

40504 RECEPTOR#  
L9 10 L8 AND RECEPTOR#

=> d ll cit ab

1. 5,753,225, May 19, 1998, Antibodies that mimic actions of neurotrophins; \*\*Douglas O. Clary\*\*, et al., 424/130.1, 141.1, 143.1, 156.1; 530/387.1, 388.1, 388.22 [IMAGE AVAILABLE]

US PAT NO: 5,753,225 [IMAGE AVAILABLE] LI:  
1 of 1

ABSTRACT:

The use and production of immunoglobulins which activate trk receptors and imitate effects of neurotrophins are provided. Immunoglobulins which block trk receptor activation and methods of use are also provided.

=> d l5 cit ab

1. 5,753,225, May 19, 1998, Antibodies that mimic actions of neurotrophins; \*\*Douglas O. Clary\*\*, et al., 424/130.1, 141.1, 143.1, 156.1; 530/387.1, 388.1, 388.22 [IMAGE AVAILABLE]

US PAT NO: 5,753,225 [IMAGE AVAILABLE] L5:  
1 of 1

ABSTRACT:

The use and production of immunoglobulins which activate trk receptors and imitate effects of neurotrophins are provided. Immunoglobulins which block trk receptor activation and methods of use are also provided.

=> d l6 cit ab 1-3

1. 5,942,428, Aug. 24, 1999, Crystals of the tyrosine kinase domain of non-insulin receptor tyrosine kinases; Moosa Mohammadi, et

al., 435/194,

69.1; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,942,428 [IMAGE AVAILABLE] L6:  
1 of 3

ABSTRACT:

Crystals of the tyrosine kinase domain of cytoplasmic tyrosine kinases and receptor tyrosine kinases that undergo ligand-mediated receptor dimerization are provided. In particular, crystals of a mutant of the tyrosine kinase domain of fibroblast growth factor receptor 1 (FLGK), alone and in complex with a non-hydrolyzable adenosine triphosphate analogue, are provided. Also provided are the high resolution three dimensional structures of crystalline FLGK, both alone and in co-complex with the adenosine triphosphate analogue, as determined by X-ray diffraction.

2. 5,734,039, Mar. 31, 1998, Antisense oligonucleotides targeting cooperating oncogenes; Bruno Calabretta, et al., 536/24.5 [IMAGE AVAILABLE]

US PAT NO: 5,734,039 [IMAGE AVAILABLE] L6:  
2 of 3

ABSTRACT:

Therapeutic combinations of two or more antisense oligonucleotides are provided. At least one first antisense oligonucleotide specific for a cytoplasmic oncogene or proto-oncogene and at least one second antisense oligonucleotide specific for a nuclear oncogene or proto-oncogene are combined for treatment of a neoplastic disease. The first antisense oligonucleotide may be specific for, e.g., a ras or raf gene, or an oncogene which codes for a protein tyrosine kinase. The nuclear gene-targeting antisense oligonucleotide preferably may be specific for a nuclear oncogene or proto-oncogene which encodes a transcriptional factor. The combined oligonucleotides have enhanced activity against neoplastic disease.

3. 5,447,860, Sep. 5, 1995, Tyrosine kinase; Steven F. Ziegler, 435/363, 194, 252.3, 254.11, 320.1; 536/23.2, 23.5 [IMAGE AVAILABLE]

US PAT NO: 5,447,860 [IMAGE AVAILABLE] L6:  
3 of 3

ABSTRACT:

A novel \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* named ork (orphan receptor tyrosine kinase) is identified and characterized. cDNA encoding the ork protein is inserted into an expression vector for production of the protein via recombinant DNA technology. The ork cDNA, when transfected into Cos-7 cells, encodes a 140 Kd protein with in vitro kinase activity. The ork gene is expressed predominantly in placenta and lung, with lower levels in umbilical vein endothelial cells, brain and kidney.

=> d l9 cit ab 1-10

1. 5,910,426, Jun. 8, 1999, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 435/68.1; 530/402 [IMAGE AVAILABLE]

US PAT NO: 5,910,426 [IMAGE AVAILABLE] L9:  
1 of 10

ABSTRACT:

The present invention is directed to a novel protein tyrosine kinase comprising a polypeptide having multiple protein kinase catalytic domains and, more particularly, two kinase catalytic domains and to

genetic sequences encoding same. Two such kinases are described and designated JAK1 and JAK2.

2. 5,882,923, Mar. 16, 1999, Glial cell line-derived neurotrophic factor regulation of ureteric budding and growth; Hannu Sariola, et al., 435/325, 368, 369, 375, 384; 514/2 [IMAGE AVAILABLE]

US PAT NO: 5,882,923 [IMAGE AVAILABLE] L9: 2 of 10

**ABSTRACT:**  
The effect of GDNF on kidney morphogenesis is disclosed. Methods for stimulating budding and branching of the ureteric epithelium, for stimulating axonal outgrowth, for maintaining ureteric epithelial cells in culture, for preventing apoptosis of ureteric epithelial cells, and for treating diseases using GDNF are also disclosed.

3. 5,852,184, Dec. 22, 1998, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 536/23.4; 435/194, 320.1; 536/23.1 [IMAGE AVAILABLE]

US PAT NO: 5,852,184 [IMAGE AVAILABLE] L9: 3 of 10

**ABSTRACT:**  
The present invention is directed to a novel protein tyrosine kinase comprising a polypeptide having multiple protein kinase catalytic domains and, more particularly, two kinase catalytic domains and to genetic sequences encoding same. Two such kinases are described and designated JAK1 and JAK2.

4. 5,821,069, Oct. 13, 1998, Method for determining tyrosine kinase in a sample; Andrew Frederick Wilks, et al., 435/7.21; 530/387.9, 388.1, 388.25, 388.26, 388.85, 389.1 [IMAGE AVAILABLE]

US PAT NO: 5,821,069 [IMAGE AVAILABLE] L9: 4 of 10

**ABSTRACT:**  
The invention relates to a method of determining the presence of a tyrosine kinase in a sample using antibodies that specifically bind to kinase active proteins. The proteins have more than one tyrosine kinase domain and no SH2 domains. Exemplary proteins are the Janus Kinases, or "JAK1" and "JAK2." Both polyclonal and monoclonal antibodies are used in the detection method.

5. 5,808,036, Sep. 15, 1998, Stem-loop oligonucleotides containing parallel and antiparallel binding domains; Eric T. Kool, 536/24.3, 435/6, 320.1, 325, 375; 536/23.1, 24.5 [IMAGE AVAILABLE]

US PAT NO: 5,808,036 [IMAGE AVAILABLE] L9: 5 of 10

**ABSTRACT:**  
The present invention provides stem-loop oligonucleotides containing a double-stranded stem domain of at least about 2 base pairs and a single-stranded loop domain. The loop domains of the present oligonucleotides include at least one parallel binding (P) domain separated by at least about 3 nucleotides from a corresponding anti-parallel binding (AP) domain. Each P and corresponding AP domain of the present oligonucleotides can bind detectably to one strand of a defined nucleic acid target wherein the P domain binds in a parallel manner to the target and the corresponding AP domain binds in an anti-parallel manner to the target. The present stem-loop oligonucleotides can bind to both single-stranded and double-stranded target nucleic acids. The present invention also provides

methods of using these oligonucleotides as well as kits and pharmaceutical compositions containing these oligonucleotides.

6. 5,716,818, Feb. 10, 1998, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 435/194, 530/326, 328, 329, 350 [IMAGE AVAILABLE]

US PAT NO: 5,716,818 [IMAGE AVAILABLE] L9: 6 of 10

**ABSTRACT:**

The present invention is directed to a novel protein tyrosine kinase comprising a polypeptide having multiple protein kinase catalytic domains and, more particularly, two kinase catalytic domains and to genetic sequences encoding same. Two such kinases are described and designated JAK1 and JAK2.

7. 5,681,714, Oct. 28, 1997, Nucleic acid encoding tek \*\*receptor\*\* tyrosine kinase; Martin L. Breitman, deceased, et al., 435/69.1, 194, 252.3, 254.1, 320.1, 325, 352, 358, 365, 367 [IMAGE AVAILABLE]

US PAT NO: 5,681,714 [IMAGE AVAILABLE] L9: 7 of 10

**ABSTRACT:**

Novel \*\*receptor\*\* tyrosine kinase protein and isoforms thereof which are expressed in cells of the endothelial lineage, and DNA segments encoding the novel protein and isoforms thereof are disclosed. Methods for identifying ligands which are capable of binding to the \*\*receptor\*\* protein and methods for screening for agonist or antagonist substances of the interaction of the protein and a ligand are also disclosed.

8. 5,658,791, Aug. 19, 1997, Antibodies which specifically bind to proteins having tyrosine kinase activity, wherein said proteins have more than one tyrosine kinase domain, and no SH2 domains; Andrew Frederick Wilks, et al., 435/331, 338; 530/387.9, 388.1, 388.25, 388.26, 388.85, 389.1 [IMAGE AVAILABLE]

US PAT NO: 5,658,791 [IMAGE AVAILABLE] L9: 8 of 10

**ABSTRACT:**

The invention relates to antibodies which specifically bind to tyrosine kinase active proteins. The proteins have more than one protein kinase domain, and no SH2 domains. Exemplary proteins are the Janus Kinases, or "JAK1" and "JAK2." Both polyclonal and monoclonal antibodies are a part of the invention, as are hybridomas which produce the monoclonal antibodies.

9. 5,514,546, May 7, 1996, Stem-loop oligonucleotides containing parallel and antiparallel binding domains; Eric T. Kool, 435/6, 536/23.1, 24.3 [IMAGE AVAILABLE]

US PAT NO: 5,514,546 [IMAGE AVAILABLE] L9: 9 of 10

**ABSTRACT:**

The present invention provides stem-loop oligonucleotides containing a double-stranded stem domain of at least about 2 base pairs and a single-stranded loop domain. The loop domains of the present oligonucleotides include at least one parallel binding (P) domain separated by at least about 3 nucleotides from a corresponding anti-parallel binding (AP) domain. Each P and corresponding AP domain of the present oligonucleotides can bind detectably to one strand of a defined nucleic acid target wherein the P domain binds in a parallel manner to the target and the corresponding AP domain binds

in an anti-parallel manner to the target. The present stem-loop oligonucleotides can bind to both single-stranded and double-stranded target nucleic acids. The present invention also provides methods of using these oligonucleotides as well as kits and pharmaceutical compositions containing these oligonucleotides.

10. 5,466,596, Nov. 14, 1995, Tissue specific transcriptional regulatory element; Martin L. Breitman, et al., 435/354, 69.1, 70.3; 536/24.1 [IMAGE AVAILABLE]

US PAT NO: 5,466,596 [IMAGE AVAILABLE] L9: 10 of 10

**ABSTRACT:**  
A novel transcriptional regulatory element which is capable of directing expression of a gene specifically in cells of the endothelial lineage. The transcriptional regulatory element may be used to target expression of a gene in cells of the endothelial lineage.

=> d l2 cit ab 1-92

1. 5,962,635, Oct. 5, 1999, Therapeutic compounds; Ahmed Abdullah Azad, et al., 530/326; 424/148.1, 160.1; 435/7.1 [IMAGE AVAILABLE]

US PAT NO: 5,962,635 [IMAGE AVAILABLE] L2: 1 of 92

**ABSTRACT:**

A biologically-active peptide fragment of the Nef protein of human immunodeficiency virus is provided, pharmaceutical compositions comprising the peptide, analogs or derivatives of the peptide and therapeutic and screening methods which utilize the peptide and compositions which comprise them. The invention is particularly useful in the suppression of the immune response or in the suppression of symptoms of autoimmune disease.

2. 5,955,594, Sep. 21, 1999, Nucleic acids encoding proteins for early liver development; Lopa Mishra, 536/23.5; 530/350, 399 [IMAGE AVAILABLE]

US PAT NO: 5,955,594 [IMAGE AVAILABLE] L2: 2 of 92

**ABSTRACT:**  
Early developing stage-specific liver proteins and the genes coding for them that have been isolated and sequenced are provided, and these genes and proteins can be utilized to diagnose and/or treat a wide variety of liver disorders and other ailments. Included in the proteins identified and isolated in the present invention are the proteins known as elf 1-3, lyor-1 (145), pk, protein 106, and praja-1, along with the nucleic acid sequences coding for these and other proteins. Since the early developing liver proteins of the invention arise during embryogenesis when the liver and other organs are in transition from an undifferentiated state to a differentiated one, these proteins are involved in tissue differentiation and thus can be utilized in methods of diagnosing and treating a variety of liver diseases and other disorders including those relating to oncogenesis and tissue repair. Accordingly, the isolated early developing liver proteins in accordance with the present invention should have implications for diagnosis and treatment of a range of diseases from end stage cirrhosis to hepatocellular carcinoma and many other disease conditions.

3. 5,955,420, Sep. 21, 1999, Rse receptor activation; Jian Chen,

et al.,  
514/2, 8, 12; 530/350, 395 [IMAGE AVAILABLE]

US PAT NO: 5,955,420 [IMAGE AVAILABLE] L2:  
3 of 92

**ABSTRACT:**  
An activator of the Rsc \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* has been identified which is encoded by growth arrest-specific gene 6 (gas6). Accordingly, the present invention provides a method of activating the Rsc receptor by exposing a cell comprising the Rsc receptor to exogenous gas6 polypeptide. Moreover, the present invention is directed to a method for enhancing the survival, proliferation or differentiation of a cell comprising a Rsc receptor by exposing the cell to exogenous gas6 polypeptide. The types of cells which can be treated according to the method include glial cells such as Schwann cells.

4. 5,955,311, Sep. 21, 1999, Monoclonal antibodies specific to VEGF receptors and uses thereof; Patricia Rockwell, et al., 435/69.1, 70.21; 530/387.3; 536/23.53 [IMAGE AVAILABLE]

US PAT NO: 5,955,311 [IMAGE AVAILABLE] L2:  
4 of 92

**ABSTRACT:**  
Monoclonal antibodies that specifically bind to an extracellular domain of a VEGF receptor and neutralize activation of the receptor are provided. In vitro and in vivo methods of using these antibodies are also provided.

5. 5,952,213, Sep. 14, 1999, Src-family kinase and methods of use thereof; Ali Hemmati-Bivandou, et al., 435/194, 252.3, 320.1, 325 [IMAGE AVAILABLE]

US PAT NO: 5,952,213 [IMAGE AVAILABLE] L2:  
5 of 92

**ABSTRACT:**  
The present invention provides a unique src-family kinase (SFK) that plays a key role in the transformation of early-stage embryonic cells to mesodermal cells. Furthermore, this src-family kinase is likely to be a proto-oncogene. The nucleic acid and amino acid sequences are disclosed.

6. 5,945,523, Aug. 31, 1999, Diagnosis and treatment of TKA-1 related disorders; Axel Ullrich, et al., 536/23.5; 435/69.1, 194, 252.3, 254.11, 320.1, 325; 536/24.31 [IMAGE AVAILABLE]

US PAT NO: 5,945,523 [IMAGE AVAILABLE] L2:  
6 of 92

**ABSTRACT:**  
The present invention relates to TKA-1 polypeptides, nucleic acids encoding such polypeptides, cells, tissues and animals containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. Methods for treatment, diagnosis, and screening are provided for TKA-1 related diseases or conditions characterized by an abnormal interaction between a TKA-1 polypeptide and a TKA-1 binding partner.

7. 5,945,522, Aug. 31, 1999, Prostate cancer gene; Daniel Cohen, et al., 435/6; 536/24.1, 24.31, 24.32, 24.33 [IMAGE AVAILABLE]

US PAT NO: 5,945,522 [IMAGE AVAILABLE] L2:  
7 of 92

**ABSTRACT:**  
The present invention relates to PG1, a gene associated with prostate

cancer. The invention also relates to methods of determining whether an individual is at risk for developing prostate cancer at a later date or whether an individual suffers from prostate cancer as a result of a mutation in the PG1 gene.

8. 5,942,602, Aug. 24, 1999, Growth factor receptor antibodies; Winfried S. Wels, et al., 530/388.22; 424/178.1; 530/387.3, 388.8, 388.85, 391.3, 391.7; 536/23.1, 24.31 [IMAGE AVAILABLE]

US PAT NO: 5,942,602 [IMAGE AVAILABLE] L2:  
8 of 92

**ABSTRACT:**  
The present invention is related to single and double chain antibodies to EGF receptor. The invention also relates to toxin conjugates of such antibodies. These antibodies are useful for treating and diagnosing the status of pathological conditions such as cancer and cellular hyperproliferation.

9. 5,942,428, Aug. 24, 1999, Crystals of the tyrosine kinase domain of non-insulin receptor tyrosine kinases; Moosa Mohammadi, et al., 435/194, 69.1; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,942,428 [IMAGE AVAILABLE] L2:  
9 of 92

**ABSTRACT:**  
Crystals of the tyrosine kinase domain of cytoplasmic tyrosine kinases and receptor tyrosine kinases that undergo ligand-mediated receptor dimerization are provided. In particular, crystals of a mutant of the tyrosine kinase domain of fibroblast growth factor receptor 1 (FLGK), alone and in complex with a non-hydrolyzable adenosine triphosphate analogue, are provided. Also provided are the high resolution three dimensional structures of crystalline FLGK, both alone and in co-complex with the adenosine triphosphate analogue, as determined by X-ray diffraction.

10. 5,939,531, Aug. 17, 1999, Recombinant antibodies specific for a growth factor receptor; Winfried Stephan Wels, et al., 530/387.3; 435/69.7; 530/387.7, 388.22, 388.8 [IMAGE AVAILABLE]

US PAT NO: 5,939,531 [IMAGE AVAILABLE] L2:  
10 of 92

**ABSTRACT:**  
The invention concerns recombinant antibodies directed to the extracellular domain of the human growth factor receptor c-erbB-2 comprising a light chain variable domain and a heavy chain variable domain of a monoclonal antibody, monoclonal antibodies directed to c-erbB-2 themselves, a method of manufacture of said recombinant antibodies and said monoclonal antibodies, hybridoma cells secreting said monoclonal antibodies, a method of manufacture of said hybridoma cells, DNA coding for the heavy chain variable domain, for the light chain variable domain and for the recombinant antibody, a method of manufacture of said DNA, hybrid vectors suitable for expression of said DNA, host cells transformed with said DNA, and the use of said recombinant antibodies and said monoclonal antibodies in the diagnosis and treatment of tumors.

11. 5,922,842, Jul. 13, 1999, Tyrosine kinase associated polypeptides; Klaus Seedorf, et al., 530/350; 435/69.1, 194; 530/300, 324 [IMAGE AVAILABLE]

US PAT NO: 5,922,842 [IMAGE AVAILABLE] L2:  
11 of 92

**ABSTRACT:**  
The present invention relates to TKA-1 polypeptides, nucleic acids encoding such polypeptides, cells, tissues and animals containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. Methods for treatment, diagnosis, and screening are provided for TKA-1 related diseases or conditions characterized by an abnormal interaction between a TKA-1 polypeptide and a TKA-1 binding partner.

12. 5,916,792, Jun. 29, 1999, Protein tyrosine kinase, JAK3; Curt I. Civin, et al., 435/194, 69.1; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,916,792 [IMAGE AVAILABLE] L2:  
12 of 92

**ABSTRACT:**  
A novel protein tyrosine kinase, JAK3, and a polynucleotide sequence encoding JAK3 polypeptide are disclosed herein. JAK3 is a new member of the JAK family of protein tyrosine kinases which are important in regulation of cellular proliferation and differentiation. Also disclosed are therapeutic methods utilizing JAK3 polypeptide and polynucleotide sequences.

13. 5,914,237, Jun. 22, 1999, Kinase receptor activation assay; Paul J. Godowski, et al., 435/7.21, 7.4, 7.94, 15; 436/501, 518, 531, 548; 530/388.22, 388.26, 389.6 [IMAGE AVAILABLE]

US PAT NO: 5,914,237 [IMAGE AVAILABLE] L2:  
13 of 92

**ABSTRACT:**  
An assay for measuring activation (i.e., autophosphorylation) of a tyrosine kinase receptor of interest is disclosed.  
(a) A first solid phase is coated with a substantially homogeneous population of cells so that the cells adhere to the first solid phase.

The cells have either an endogenous tyrosine kinase receptor or have been transformed with DNA encoding a receptor or "receptor construct"

and the DNA has been expressed so that the receptor or receptor construct is presented in the cell membranes of the cells.

(b) A ligand is then added to the solid phase having the adhering cells,

such that the tyrosine kinase receptor is exposed to the ligand.

(c) Following exposure to the ligand, the adherent cells are solubilized, thereby releasing cell lysate.

(d) A second solid phase is coated with a capture agent which binds

specifically to the tyrosine kinase receptor, or, in the case of a receptor construct, to the flag polypeptide.

(e) The cell lysate obtained in step (c) is added to the wells containing the adhering capture agent so as to capture the receptor or receptor construct to the wells.

(f) A washing step is then carried out, so as to remove unbound cell lysate, leaving the captured receptor or receptor construct.

(g) The captured receptor or receptor construct is exposed to a labelled anti-phosphotyrosine antibody which identifies phosphorylated residues

in the tyrosine kinase receptor.

(h) Binding of the anti-phosphotyrosine antibody to the captured receptor or receptor construct is measured.

14. 5,912,326, Jun. 15, 1999, Cerebellum-derived growth factors; Han Chang, 530/399, 350 [IMAGE AVAILABLE]

US PAT NO: 5,912,326 [IMAGE AVAILABLE] L2:  
14 of 92

**ABSTRACT:**  
The present invention relates to the discovery of a novel erbB receptor ligand, referred to hereinafter as "cdGF", which protein has

apparently broad involvement in the formation and maintenance of ordered spatial arrangements of differentiated tissues in vertebrates, and can be used to generate and/or maintain an array of different vertebrate tissue both in vitro and in vivo.

15. 5,912,183, Jun. 15, 1999, Peptide inhibitors of mitogenesis and motogenesis; Paolo Comoglio, et al., 436/501; 530/300, 324, 326 [IMAGE AVAILABLE]

US PAT NO: 5,912,183 [IMAGE AVAILABLE] L2:  
15 of 92

**ABSTRACT:**  
The invention in the field of cell biology relates to novel peptides able to interact with intracellular signal transducers, thus interfering with signal transduction pathways leading to cell proliferation and motility.  
The peptides of the invention may be chemically synthesized from single amino acids and/or preformed peptides of two or more amino acid residues.  
The peptides of the invention find an useful application in the treatment of a neoplastic disease.

16. 5,912,160, Jun. 15, 1999, Gab1, Grb2 binding protein, and compositions for making and methods of using the same; Albert J. Wong, et al., 435/252.3, 69.1, 320.1; 530/350; 536/23.5, 24.3 [IMAGE AVAILABLE]

US PAT NO: 5,912,160 [IMAGE AVAILABLE] L2:  
16 of 92

**ABSTRACT:**  
A substantially pure protein, Gab1, that binds to Grb2 is disclosed.  
Isolated nucleic acid molecules that encode Gab1 is disclosed.  
Pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with nucleic acid molecules are disclosed.  
Fragments of nucleic acid molecules that encode Gab1 having at least 10 nucleotides and oligonucleotide molecule comprising a nucleotide sequence complementary to a nucleotide sequence of at least 10 nucleotides are disclosed. Recombinant expression vectors that comprise the nucleic acid molecule that encode Gab1, and host cells that comprise such recombinant vectors are disclosed. Antibodies that bind to an epitope on Gab1 are disclosed. Methods of identifying inhibitors, activators and substrates of Gab1 are disclosed. Antisense compounds and methods of using the same are disclosed.

17. 5,912,133, Jun. 15, 1999, Method for isolating stem cells expressing flk-1 receptors; Ihor R. Lemischka, 435/7.21, 971; 530/388.7, 389.6 [IMAGE AVAILABLE]

US PAT NO: 5,912,133 [IMAGE AVAILABLE] L2:  
17 of 92

**ABSTRACT:**  
Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are provided. Also included are the receptors encoded by such nucleic acid molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1a (murine flk-2), FIG. 1b (human flk-2) and FIG. 2 (murine flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1a, FIG. 1b and FIG. 2; ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the

proliferation and/or differentiation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

18. 5,910,574, Jun. 8, 1999, Human trk receptors and neurotrophic factor inhibitors; Leonard G. Presta, et al., 530/388.22; 424/133.1, 143.1; 530/387.3, 388.1 [IMAGE AVAILABLE]

US PAT NO: 5,910,574 [IMAGE AVAILABLE] L2:  
18 of 92

**ABSTRACT:**  
The invention concerns human trkB and trkC receptors and their functional derivatives. The invention further concerns immunoadhesins comprising trk receptor sequences fused to immunoglobulin sequences.

19. 5,895,813, Apr. 20, 1999, Diagnosis and treatment of TKA-1 related disorders; Axel Ullrich, et al., 536/23.5; 435/252.3, 254.11, 320.1, 325; 536/24.1, 24.3 [IMAGE AVAILABLE]

US PAT NO: 5,895,813 [IMAGE AVAILABLE] L2:  
19 of 92

**ABSTRACT:**  
The present invention relates to TKA-1 polypeptides, nucleic acids encoding such polypeptides, cells, tissues and animals containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. Methods for treatment diagnosis, and screening are provided for TKA-1 related diseases or conditions characterized by an abnormal interaction between a TKA-1 polypeptide and a TKA-1 binding partner.

20. 5,891,650, Apr. 6, 1999, Kinase receptor activation assay; Paul J. Godowski, et al., 435/7.21, 7.4, 7.94, 15; 436/501, 518, 531, 548, 530/388.22, 388.26, 389.6 [IMAGE AVAILABLE]

US PAT NO: 5,891,650 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**  
An assay for measuring activation (i.e., autophosphorylation) of a tyrosine kinase receptor of interest is disclosed.  
(a) A first solid phase is coated with a substantially homogeneous population of cells so that the cells adhere to the first solid phase.  
The cells have either an endogenous tyrosine kinase receptor or have been transformed with DNA encoding a receptor or "receptor construct" and the DNA has been expressed so that the receptor or receptor construct is presented in the cell membranes of the cells.  
(b) A ligand is then added to the solid phase having the adhering cells, such that the tyrosine kinase receptor is exposed to the ligand.  
(c) Following exposure to the ligand, the adherent cells are solubilized, thereby releasing cell lysate.  
(d) A second solid phase is coated with a capture agent which binds specifically to the tyrosine kinase receptor, or, in the case of a receptor construct, to the flag polypeptide.  
(e) The cell lysate obtained in step (c) is added to the wells containing the adhering capture agent so as to capture the receptor or receptor construct to the wells.  
(f) A washing step is then carried out, so as to remove unbound cell lysate, leaving the captured receptor or receptor construct.  
(g) The captured receptor or receptor construct is exposed to a labelled anti-phosphotyrosine antibody which identifies phosphorylated residues in the tyrosine kinase receptor.  
(h) Binding of the anti-phosphotyrosine antibody to the captured

receptor or receptor construct is measured.

21. 5,888,794, Mar. 30, 1999, Receptor-type phosphotyrosine phosphatase-alpha; Joseph Schlessinger, et al., 435/196; 424/94.6 [IMAGE AVAILABLE]

US PAT NO: 5,888,794 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**  
A novel receptor-type protein tyrosine phosphatase (RPTP) protein or glycoprotein and the DNA coding therefor is expressed in a wide variety of mammalian tissues. Included in this family of proteins are human RPTP.alpha., human RPTP.beta. and human RPTP.gamma.. The RPTP protein or glycoprotein may be produced by recombinant means. Antibodies to the proteins, methods for measuring the quantity of the proteins, methods for screening compounds, such as drugs, which can bind to the proteins and inhibit or stimulate their activity, are provided.

22. 5,883,110, Mar. 16, 1999, Pharmaceutical compositions and methods for modulating signal transduction; Peng Cho Tang, et al., 514/342, 363, 369; 548/184 [IMAGE AVAILABLE]

US PAT NO: 5,883,110 [IMAGE AVAILABLE] L2:  
22 of 92

**ABSTRACT:**  
The present invention relates to organic molecules capable of inhibiting protein tyrosine phosphatase activity. The invention further relates to the use of such molecules to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity. Finally, the invention relates to the use of such molecules to treat various disease states including diabetes mellitus.

23. 5,880,153, Mar. 9, 1999, Method for upregulation of TRKB and TRKC receptors in central nervous system neurons; Toomas Neuman, et al., 514/557 [IMAGE AVAILABLE]

US PAT NO: 5,880,153 [IMAGE AVAILABLE] L2:  
23 of 92

**ABSTRACT:**  
The present invention provides compositions and methods for inducing expression of neurotrophic factor receptors trkB and trkC in neurons. The compositions include a material that activates a nuclear hormone receptor, a material that activates the second messenger response system, and a material that elevates Ca.sup.2+.

24. 5,877,016, Mar. 2, 1999, Human trk receptors and neurotrophic factor inhibitors; Leonard G. Presta, et al., 435/325, 69.1, 320.1; 530/387.3, 388.22; 536/23.4 [IMAGE AVAILABLE]

US PAT NO: 5,877,016 [IMAGE AVAILABLE] L2:  
24 of 92

**ABSTRACT:**  
The invention concerns human trkB and trkC receptors and their functional derivatives. The invention further concerns immunoadhesins comprising trk receptor sequences fused to immunoglobulin sequences.

25. 5,874,542, Feb. 23, 1999, Single chain antibodies specific to VEGF receptors; Patricia Rockwell, et al., 530/387.3, 388.22 [IMAGE AVAILABLE]

US PAT NO: 5,874,542 [IMAGE AVAILABLE] L2:  
25 of 92

**ABSTRACT:**  
Monoclonal antibodies that specifically bind to an extracellular domain of a VEGF receptor and neutralize activation of the receptor are

provided. In vitro and in vivo methods of using these antibodies are also provided.

26. 5,872,223, Feb. 16, 1999, Immunoconjugates comprising tyrosine kinase inhibitors; Fatih M. Uckun, 530/391.1, 391.7, 391.9, 402, 403 [IMAGE AVAILABLE]

US PAT NO: 5,872,223 [IMAGE AVAILABLE] L2: 26 of 92

**ABSTRACT:**  
Immunoconjugates effective for treating cancers and autoimmune diseases in humans are provided which comprise a tyrosine kinase inhibitor linked to a ligand targeting a cell surface receptor which are specifically capable of inhibiting receptor associated tyrosine kinases.

27. 5,872,102, Feb. 16, 1999, Method for isolation of bovine low-molecular weight CR-binding substance and method of use of the same; John B. Vincent, et al., 514/21; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,872,102 [IMAGE AVAILABLE] L2: 27 of 92

**ABSTRACT:**  
A fully chromium loaded bovine low-molecular weight chromium-binding protein is isolated by a process that combines homogenization with supplementation of chromium content. Following homogenization with water, the homogenate is fractionated with ethanol, and the fractions obtained are subjected to serial chromatography (ion-exchange followed by size-exclusion chromatography) to obtain the biologically pure bovine LMWCr. This biologically pure material elutes from an HPLC column as essentially a single band, giving a high degree of purity. The LMWCr is useful as a dietary supplement, and for the treatment or prevention of a variety of chromium-related disease conditions.

28. 5,869,485, Feb. 9, 1999, Pyrrolo[2,3-d]pyrimidines and their use; Martin Missbach, 514/234.2, 258; 544/117, 280; 548/558 [IMAGE AVAILABLE]

US PAT NO: 5,869,485 [IMAGE AVAILABLE] L2: 28 of 92

**ABSTRACT:**

The invention relates to the use of the compounds mentioned below in the therapeutic treatment of tumor diseases and other proliferative diseases, such as psoriasis, and to novel compounds of that type. The compounds are compounds of formula I ##STR1## wherein n is from 0 to 5 and, when n is not 0, R is one or more substituents selected from halogen, alkyl, trifluoromethyl and alkoxy; and R<sub>1</sub> and R<sub>2</sub> are each independently of the other alkyl, or phenyl that is unsubstituted or substituted by halogen, trifluoromethyl, alkyl or by alkoxy, it also being possible for one of the two radicals R<sub>1</sub> and R<sub>2</sub> to be hydrogen, or R<sub>1</sub> and R<sub>2</sub> together form an alkylene chain having from 2 to 5 carbon atoms that is unsubstituted or substituted by alkyl; or salts thereof. Compounds of formula I inhibit protein kinases, for example the tyrosine protein kinase of the receptor for the epidermal growth factor, EGF.

29. 5,864,020, Jan. 26, 1999, HTk ligand; Brian D. Bennett, et al., 530/388.24; 435/188; 530/387.1, 391.1, 391.3 [IMAGE AVAILABLE]

US PAT NO: 5,864,020 [IMAGE AVAILABLE] L2: 29 of 92

**ABSTRACT:**  
A novel hepatoma transmembrane kinase receptor ligand (Htk

ligand) which binds to, and activates, the Htk receptor is disclosed. As examples, mouse and human Htk ligands have been identified in a variety of tissues using a soluble Htk-Fc fusion protein. The ligands have been cloned and sequenced. The invention also relates to nucleic acids encoding the ligand, methods for production and use of the ligand, and antibodies directed thereto.

30. 5,861,499, Jan. 19, 1999, Nucleic acid molecules encoding the variable or hypervariable region of a monoclonal antibody that binds to an extracellular domain; Patricia Rockwell, et al., 536/23.53; 530/388.1, 388.24, 389.2 [IMAGE AVAILABLE]

US PAT NO: 5,861,499 [IMAGE AVAILABLE] L2: 30 of 92

**ABSTRACT:**  
Nucleic acid molecules comprising a nucleic acid sequence that encodes an amino acid sequence wherein the amino acid sequence consists of the variable region or of the hypervariable region of a monoclonal antibody that specifically binds to an extracellular domain of a VEGF receptor and neutralizes activation of the receptor.

31. 5,861,266, Jan. 19, 1999, Treatment of diabetes mellitus and insulin receptor signal transduction; Axel Ullrich, et al., 435/21; 424/130.1, 195.1; 435/184; 514/2, 866 [IMAGE AVAILABLE]

US PAT NO: 5,861,266 [IMAGE AVAILABLE] L2: 31 of 92

**ABSTRACT:**  
The present invention relates to novel modalities of treatment of diabetes, and other diseases caused by dysfunctional signal transduction by insulin receptor type tyrosine kinases (IR-PTK). Applicants discovered that IR-PTK activity may be modified by modulating the activity of a tyrosine phosphatase, and IR-PTK signal transduction may be triggered even in the absence of ligand. Methods for identifying compounds that, by modulating RPTP.alpha. or RPTP.epsilon. activity, elicit or modulate insulin receptor signal transduction are also described.

32. 5,861,239, Jan. 19, 1999, Methods for identifying compounds that modulate mammalian tub protein activity; Patrick W. Kleyn, et al., 435/4 [IMAGE AVAILABLE]

US PAT NO: 5,861,239 [IMAGE AVAILABLE] L2: 32 of 92

**ABSTRACT:**  
The present invention relates to the identification of novel nucleic acid molecules and proteins encoded by such nucleic acid molecules or degenerate variants thereof, that participate in the control of mammalian body weight. The nucleic acid molecules of the present invention represent the gene corresponding to the mammalian tub gene, a gene that is involved in the regulation of body weight. The present invention also relates to methods for identifying compounds that modulate tub protein activity.

33. 5,856,111, Jan. 5, 1999, Methods for identifying modulators of insulin receptor phosphorylation; Axel Ullrich, et al., 435/7.21, 15, 21, 69.1, 194, 196, 325; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,856,111 [IMAGE AVAILABLE] L2: 33 of 92

**ABSTRACT:**

The present invention relates to cell lines useful for the screening and identification of compounds that by modulating phosphotyrosine phosphatase activity, modulate insulin receptor type tyrosine kinase mediated signal transduction. Genetically engineered cells expressing IR in culture overcome the effect of insulin on morphology and adhesion when they are also coexpressing RPTP.alpha. or RPTP.epsilon.. Such engineered cell lines may be used to screen and identify non-toxic compounds that could elicit or modulate insulin signal transduction even in the absence of insulin.

34. 5,854,388, Dec. 29, 1998, Angiotensin IV peptides and receptor; Joseph W. Harding, et al., 530/329; 436/548; 514/17, 18; 530/330, 331, 387.2, 387.9, 388.24 [IMAGE AVAILABLE]

US PAT NO: 5,854,388 [IMAGE AVAILABLE] L2: 34 of 92

**ABSTRACT:**

A unique and novel angiotensin AT4 receptor and AIV ligand system for binding a small N-terminal hexapeptide fragment of Angiotensin II (referred to as AIV, with amino acid sequence Val.sub.1 -Tyr.sub.2 -Ile.sub.3 -His.sub.4 -Pro.sub.5 -Phe.sub.6 ; SEQ. ID. NO. 1) is disclosed. AIV ligand binds saturably, reversibly, specifically, and with high affinity to membrane AT4 receptors in a variety of tissues, including heart, lung, kidney, aorta, brain, liver, and uterus, from many animal species. The AT4 receptor is pharmacologically distinct from classic angiotensin receptors (AT1 or AT2). The system employs AIV or C-terminally truncated or extended AIV-like peptides (e.g., VYIHPFX; SEQ. ID. NO. 8) as the signaling agent, and the AT4 plasma membrane receptor as the detection mechanism. The angiotensin AT4 receptor and receptor fragments (including the receptor binding site domain) are capable of binding a VYIHPF (SEQ. ID. NO. 1) angiotensin AIV N-terminal peptide but not an angiotensin AI or AII N-terminal peptide, i.e., DRVYIHPF (SEQ. ID. NO. 2) or RVYIHPF (SEQ. ID. NO. 3), respectively. Also disclosed are processes for isolating angiotensin AT4 receptor and AIV angiogeninase, identifying angiotensin AIV agonists and antagonists, and constructing diagnostic assays to specifically measure AIV and AI-specific angiotensinase in biological fluids.

35. 5,854,045, Dec. 29, 1998, Transmembrane tyrosine phosphatase and methods of use thereof; Kathy S. Fang, et al., 435/196, 69.1; 530/300, 326, 536/23.2 [IMAGE AVAILABLE]

US PAT NO: 5,854,045 [IMAGE AVAILABLE] L2: 35 of 92

**ABSTRACT:**

The present invention relates to regulation and control of cellular processes by transmembrane protein tyrosine phosphatases, and to ligands that agonize or antagonize tyrosine phosphorylation mediated by such tyrosine phosphatases. This invention further relates to diagnosis and therapy based on the activity of such ligands. In particular, the invention provides a novel transmembrane protein tyrosine phosphatase-lambda. (PTP.lambda.), nucleic acids encoding the same, antibodies to the PTP.lambda., and methods for identifying ligands to the PTP.lambda. of the invention. A specific Example describes the isolation and characterization of the first chicken transmembrane PTP, called ChPTP.lambda.. It has a unique extracellular domain containing a Ser/Thr/Pro-rich region, spectrin-like repeats, a fibronectin III

domain, and an alternatively spliced N-terminus. The expression of ChPTP.lambda. in various tissues and cells was also examined. ChPTP.lambda. was shown to have a tyrosine-specific phosphatase activity, and the basic characteristics of this enzyme were studied.

36. 5,846,824, Dec. 8, 1998, Polypeptides having kinase activity, their preparation and use; Ian D. Hiles, et al., 435/348, 320.1, 325, 536/23.2, 24.3 [IMAGE AVAILABLE]

US PAT NO: 5,846,824 [IMAGE AVAILABLE] L2: 36 of 92

**ABSTRACT:**  
This invention relates to new polypeptides which exhibit kinase activity or, more specifically, which show phosphoinositide (PI) 3-kinase activity. Such polypeptides are involved in pathways responsible for cellular growth and differentiation. An isolated polypeptide which possesses PI3-kinase activity when produced by recombinant production in insect cells is disclosed.

37. 5,844,092, Dec. 1, 1998, Human TRK receptors and neurotrophic factor inhibitors; Leonard G. Presta, et al., 530/387.3; 424/133.1; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,844,092 [IMAGE AVAILABLE] L2: 37 of 92

**ABSTRACT:**  
The invention concerns human trkB and trkC receptors and their functional derivatives. The invention further concerns immunoadhesins comprising trk receptor sequences fused to immunoglobulin sequences.

38. 5,840,301, Nov. 24, 1998, Methods of use of chimerized, humanized, and single chain antibodies specific to VEGF receptors; Patricia Rockwell, et al., 424/143.1, 133.1, 135.1; 530/387.3, 388.1, 388.22 [IMAGE AVAILABLE]

US PAT NO: 5,840,301 [IMAGE AVAILABLE] L2: 38 of 92

**ABSTRACT:**  
Monoclonal antibodies that specifically bind to an extracellular domain of a VEGF receptor and neutralize activation of the receptor are provided. In vitro and in vivo methods of using these antibodies are also provided.

39. 5,837,815, Nov. 17, 1998, PYK2 related polypeptide products; Sima Lev, et al., 530/350; 435/69.1; 530/412 [IMAGE AVAILABLE]

US PAT NO: 5,837,815 [IMAGE AVAILABLE] L2: 39 of 92

**ABSTRACT:**  
The present invention features a method for treatment of an organism having a disease or condition characterized by an abnormality in a signal transduction pathway, wherein the signal transduction pathway include a PYK2 protein. The invention also features methods for diagnosing such diseases and for screening for agents that will be useful in treating such diseases. The invention also features purified and/or isolated nucleic acid encoding a PYK2 protein.

40. 5,837,524, Nov. 17, 1998, PYK2 related polynucleotide products; Joseph Schlessinger, et al., 435/252.3, 91.4, 320.1; 536/23.1, 25.4 [IMAGE AVAILABLE]

US PAT NO: 5,837,524 [IMAGE AVAILABLE] L2: 40 of 92

**ABSTRACT:**  
The present invention features a method for treatment of an

organism having a disease or condition characterized by an abnormality in a signal transduction pathway, wherein the signal transduction pathway includes a PYK2 protein. The invention also features methods for diagnosing such diseases and for screening for agents that will be useful in treating such diseases. The invention also features purified and/or isolated nucleic acid encoding a PYK2 protein.

41. 5,837,448, Nov. 17, 1998, Protein-tyrosine kinase genes; Greg E. Lemke, et al., 435/6, 252.3, 320.1, 325, 352; 536/23.5, 24.31, 24.33 [IMAGE AVAILABLE]

US PAT NO: 5,837,448 [IMAGE AVAILABLE] L2: 41 of 92

**ABSTRACT:**  
The invention provides pure "receptor" "protein" "tyrosine" "kinase" (PTK) subtypes, tyro-1-8 and tyro-10-12, polynucleotides encoding these PTK subtypes and the use of oligonucleotides which align with the flanking regions of the receptor PTK subtypes, thereby allowing amplification of the polynucleotides encoding the receptor PTK subtype.

42. 5,824,492, Oct. 20, 1998, Polypeptides having kinase activity, their preparation and use; Ian D. Hiles, et al., 435/15, 29, 194 [IMAGE AVAILABLE]

US PAT NO: 5,824,492 [IMAGE AVAILABLE] L2: 42 of 92

**ABSTRACT:**

This invention relates to new polypeptides which exhibit kinase activity or, more specifically, which show phosphoinositide (PI) 3-kinase activity. Such polypeptides are involved in pathways responsible for cellular growth and differentiation. An isolated polypeptide which possesses PI3-kinase activity when produced by recombinant production in insect cells is disclosed.

43. 5,814,511, Sep. 29, 1998, Human breast epithelial cell type with stem cell and luminal epithelial cell characteristics; Chia-Cheng Chang, et al., 435/371, 378, 380, 387, 405, 406 [IMAGE AVAILABLE]

US PAT NO: 5,814,511 [IMAGE AVAILABLE] L2: 43 of 92

**ABSTRACT:**  
Described is a substantially purified human breast epithelial cell (Type I HBEC) displaying the following characteristics: variable cell shape; smooth cell colony boundary; deficiency in gap junctional intercellular communication; positive expression of epithelial membrane antigen and keratin 18; negative expression of keratin 14, alpha.6 integrin and gap junction genes for connexins (Cx26, Cx32 and Cx43); growth promotion by fetal bovine serum; induction by cholera toxin to differentiate into Type II HBEC (prior art); and acquisition anchorage independent growth by Semian virus 40 transfection. Also described is a method of obtaining the above-identified epithelial cells comprising the steps of: a) development of a mixture of human breast epithelial cells from reduction mammoplasty tissues using the MSU-1 medium; b) eliminating stromal fibroblasts by a trypsin (0.002%) and ethylenediamine tetraacetic acid (0.02%) solution; c) separating Type I HBEC from Type II HBEC which attach on culture dishes earlier by collecting Type I HBEC that remain in suspension after

trypsinization and prolonged incubation; d) the continuing culture of these cells in MSU-1 medium supplemented with fetal bovine serum, which inhibits the growth of Type II HBEC while promoting the growth of Type I HBEC, gives rise to Type I HBEC. Described also is a new defined medium (the MSU-1 medium) which supports the growth of both Type I and Type II human breast epithelial cells.

44. 5,814,479, Sep. 29, 1998, Bsk receptor-like tyrosine kinase; Renping Zhou, et al., 435/69.1, 194, 252.3, 254.11, 320.1, 325, 348; 536/23.2, 23.5, 24.31 [IMAGE AVAILABLE]

US PAT NO: 5,814,479 [IMAGE AVAILABLE] L2: 44 of 92

**ABSTRACT:**  
The present invention provides a nucleic acid sequence encoding a receptor-like tyrosine kinase designated, Bsk. The Bsk receptor-like tyrosine kinase is expressed predominantly in the brain, specifically the limbic system. Also included is the receptor encoded by the Bsk nucleic acid sequence and antibodies reactive with the Bsk protein. This invention further relates to bioassays using the nucleic acid sequence, receptor protein or antibodies of this invention to diagnose, assess, or prognose a mammal afflicted with neurodegenerative disease. Therapeutic uses for the Bsk receptor-like tyrosine kinase are also provided. This invention also relates to the ligand for the Bsk receptor, and diagnostic and therapeutic uses for the Bsk ligand.

45. 5,811,516, Sep. 22, 1998, Tyro-3 protein tyrosine kinase; Greg E. Lemke, et al., 530/350; 435/6; 530/300 [IMAGE AVAILABLE]

US PAT NO: 5,811,516 [IMAGE AVAILABLE] L2: 45 of 92

**ABSTRACT:**  
A novel protein tyrosine kinase (PTK) designated tyro-3 is provided herein. Polynucleotides encoding tyro-3 are also provided. Tyro-3 is identified and characterized as being expressed in brain tissue.

46. 5,807,989, Sep. 15, 1998, Methods for treatment or diagnosis of diseases or disorders associated with an APB domain; Benjamin Lewis Margolis, et al., 530/350; 436/64 [IMAGE AVAILABLE]

US PAT NO: 5,807,989 [IMAGE AVAILABLE] L2: 46 of 92

**ABSTRACT:**  
The present invention concerns methods for diagnosis and treatment of diseases or disorders characterized by abnormal cellular signal transduction involving a newly identified region, herein termed the "APB domain." APB domain binding between proteins is believed to play an important role in signal transduction pathways and, thereby, influence cellular events. Thus, APB mediated activity plays a role in signal transduction pathways and agents modulating APB mediated activity can be used to treat diseases or disorders involving proteins containing APB domains.

47. 5,798,374, Aug. 25, 1998, Methods of inhibiting phosphatase activity and treatment of disorders associated therewith; Peng Cho Tang, et al., 514/369; 548/184 [IMAGE AVAILABLE]

US PAT NO: 5,798,374 [IMAGE AVAILABLE] L2: 47 of 92

**ABSTRACT:**  
The present invention relates to organic molecules capable of inhibiting

protein tyrosine phosphatase activity. The invention further relates to the use of such molecules to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity. Finally, the invention relates to the use of such molecules to treat various disease states including diabetes mellitus.

48. 5,786,454, Jul. 28, 1998, Modified SH2 domains; Gabriel Waksman, et al., 530/402, 350 [IMAGE AVAILABLE]

US PAT NO: 5,786,454 [IMAGE AVAILABLE] L2:  
48 of 92

**ABSTRACT:**  
Modified SH2 domains of intracellular proteins and methods of use, wherein the SH2 domains are modified to include an altered binding site for a signal transduction protein. The binding site is altered to either change the specificity of the SH2 domain for a signal transduction protein that is not the natural ligand or to include a reactive group, such as a reactive amino acid, that reacts with a phosphorylated amino acid of the signal transduction protein. The modified SH2 domains are useful as research tools or in methods for inactivating or inhibiting signal transduction proteins, especially those that contribute to disease or disorders such as cancer or for targeting specific SH2 domains for diagnostics.

49. 5,783,186, Jul. 21, 1998, Antibody-induced apoptosis; Tsutomu Arakawa, et al., 424/143.1, 133.1, 138.1, 141.1, 142.1; 435/330, 366; 530/387.3, 387.7, 388.15, 388.2, 388.22, 388.8, 388.85, 389.7 [IMAGE AVAILABLE]

US PAT NO: 5,783,186 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**  
Anti-Her2 antibodies which induce apoptosis in Her2 expressing cells are disclosed. The antibodies are used to "tag" Her2 overexpressing tumors for elimination by the host immune system. Also disclosed are hybridoma cell lines producing the antibodies, methods for treating cancer using the antibodies, and pharmaceutical compositions.

50. 5,780,496, Jul. 14, 1998, Method and compositions for inhibition of adaptor protein/tyrosine kinase interactions; Peng Cho Tang, et al., 514/414; 548/455 [IMAGE AVAILABLE]

US PAT NO: 5,780,496 [IMAGE AVAILABLE] L2:  
50 of 92

**ABSTRACT:**  
The present invention relates to methods and compositions for the inhibition of adaptor protein/protein tyrosine kinase protein interactions, especially wherein those interactions involving a protein tyrosine kinase capable of completing with a member of the SH2- and/or SH3-containing family of adaptor proteins are associated with a cell proliferative disorder. Specifically, the present invention relates to particular compounds, especially quinazoline derivative compounds, and methods utilizing such compounds.

51. 5,770,567, Jun. 23, 1998, Sensory and motor neuron derived factor (SMDF); Wei-Hsien Ho, et al., 514/12, 2; 530/350, 395, 399 [IMAGE AVAILABLE]

US PAT NO: 5,770,567 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**

Isolated SMDF, isolated DNA encoding SMDF, and recombinant or synthetic methods of preparing SMDF are disclosed. SMDF contains a .beta.-type EGF-like domain and a N-terminal sequence which is distinct from all neuregulins reported so far. SMDF, when expressed in recombinant cell culture, activates tyrosine phosphorylation of the HER2/neu receptor in human breast cancer cells and displays mitogenic activity on Schwann cells. Northern blot and in situ hybridization analysis show that SMDF differs from other neuregulins in that it is nervous tissue

specific, and is very highly expressed, in comparison to other neuregulins, in the human and rat spinal cord motor neurons and sensory neurons.

54. 5,760,041, Jun. 2, 1998, 4-aminoquinazoline EGFR Inhibitors; Allan Wissner, et al., 514/259; 544/293 [IMAGE AVAILABLE]

US PAT NO: 5,760,041 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**

This invention provides a compound having the formula ##STR1## wherein: X is phenyl which is optionally substituted; R and R<sub>sub.1</sub> are each, independently, hydrogen, halogen, alkyl, alkoxy, hydroxy, or trifluoromethyl; R<sub>sub.2</sub> is hydrogen, alkyl, alkoxy, hydroxy, trifluoromethyl; Y is a radical selected from the group consisting of ##STR2## R<sub>sub.3</sub> is independently hydrogen, alkyl, carboxy, carboalkoxy, phenyl, or carboxalkyl; n=2-4; or a pharmaceutically acceptable salt thereof, with the proviso that each R<sub>sub.3</sub> of Y may be the same or different which are useful as antineoplastic agents.

55. 5,756,456, May 26, 1998, Methods involving sensory and motor neuron derived factor (SMDF); Wei-Hsien Ho, et al., 514/12, 2 [IMAGE AVAILABLE]

US PAT NO: 5,756,456 [IMAGE AVAILABLE] L2:  
55 of 92

**ABSTRACT:**

A method for activating the HER2 receptor comprising contacting a cell which expresses this receptor with SMDF polypeptides is disclosed. A method for enhancing differentiation and/or proliferation of a cell using SMDF polypeptides is also disclosed. These methods may be performed in vitro or in vivo.

56. 5,750,365, May 12, 1998, Isolated nucleic acid encoding a newt acidic fibroblast growth factor (aFGF); Ing Ming Chiu, et al., 435/69.1, 69.4, 252.3, 320.1; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,750,365 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**

The present invention relates to novel newt aFGF cDNA and sequence, newt FGFR1 cDNA and sequence, newt FGFR2 cDNA and sequence, newt FGFR3 cDNA and sequence, newt KGFR cDNA and sequence, and CHO-KL cell line (KPT12-2) expressing newt KGFR. Mutant cell lines (Tr31-5-1 and Tr33-1-2) that become non-responsive to aFGF stimulation are used to differentiate biological activities among different forms of aFGF and other FGF proteins. These novel sequences and cell lines substantially enhance the availability of newt acidic fibroblast growth factor and are useful for producing compositions for promoting growth and/or wound healing.

57. 5,747,651, May 5, 1998, Antibodies against tyrosine kinase receptor flk-1; Ihor R. Lemischka, 530/387.9, 388.22, 388.7, 389.1, 389.6 [IMAGE AVAILABLE]

US PAT NO: 5,747,651 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**

Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are provided. Also included are the receptors encoded by such nucleic acid

molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1a (murine flk-2), FIG. 1b (human flk-2) and FIG. 2 (murine flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1a, FIG. 1b and FIG. 2; ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the proliferation and/or differentiation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

58. 5,741,689, Apr. 21, 1998, Methods to inhibit serine kinase activity and to alter intersubunit binding activity of phosphatidylinositol 3-kinase, and serine kinase active sequence of the same; Ritu Bala Dhand, et al., 435/194, 424/139.1; 435/252.3, 320.1, 331, 338; 536/23.1, 24.1 [IMAGE AVAILABLE]

US PAT NO: 5,741,689 [IMAGE AVAILABLE] L2: 58 of 92

**ABSTRACT:**  
The invention provides for a method to inhibit the binding between the p85 and p110 subunits of said PI3-kinase and thus a method to modulate PI3-kinase activity and modulate the response of cells to external stimuli. In particular, disabling, by conventional means, residues located in the inter-SH2 domain of said p85 subunit, specifically a region containing amino acid residue 478 to amino acid residue 513 of p85.alpha. subunit, or amino acid residue 445 to amino acid residue 485 of p85.beta. subunit of said PI3-kinase. Interference with these binding regions will affect binding between the subunits and results in inhibiting PI3-kinase activity. This invention further relates to a methods to modulate the serine kinase activity of the PI3-kinase which can be achieved by disabling the DRHNSN sequence of the p110 subunit and can also be used to effect changes in overall PI3-kinase activity. This invention is further related to an (ant)agonist which affects serine kinase activity of PI3-kinase. An agonist is provided which stimulates the phosphorylation of the p85 subunit at the serine residue at position 608, wherein phosphorylation at the serine residue indirectly results in inhibiting PI3-kinase activity.

59. 5,734,039, Mar. 31, 1998, Antisense oligonucleotides targeting cooperating oncogenes; Bruno Calabretta, et al., 536/24.5 [IMAGE AVAILABLE]

US PAT NO: 5,734,039 [IMAGE AVAILABLE] L2: 59 of 92

**ABSTRACT:**  
Therapeutic combinations of two or more antisense oligonucleotides are provided. At least one first antisense oligonucleotide specific for a cytoplasmic oncogene or proto-oncogene and at least one second antisense oligonucleotide specific for a nuclear oncogene or proto-oncogene are combined for treatment of a neoplastic disease. The first antisense oligonucleotide may be specific for, e.g., a ras or raf gene, or an oncogene which codes for a protein tyrosine kinase. The nuclear gene-targeting antisense oligonucleotide preferably may be specific for a nuclear oncogene or proto-oncogene which encodes a

transcriptional factor. The combined oligonucleotides have enhanced activity against neoplastic disease.

60. 5,728,536, Mar. 17, 1998, Jak kinases and regulation of Cytokine signal transduction; James N. Ihle, et al., 435/7.21, 7.4, 7.72; 436/518 [IMAGE AVAILABLE]

US PAT NO: 5,728,536 [IMAGE AVAILABLE] L2: 60 of 92

**ABSTRACT:**  
The present invention is based on the discovery that a critical step in the cellular response to several cytokines is the activation (i.e. tyrosine phosphorylation) of a member of the Jak kinase family. In particular, several cytokines whose activity is mediated by the activation of Jak2 kinase are identified. The present invention provides novel methods for regulating the cellular response to these cytokines by inhibiting or enhancing the Jak kinase activity which mediates the response. Assays for identifying inhibitors of Jak kinase activity or cytokine-induced Jak kinase activation useful in the methods of the invention are also provided. Antibodies raised against peptide fragments of Jak1, Jak2, and Tyk2 kinase capable of specifically binding to these Jak kinases without interfering with kinase activity are also provided. In addition, the complete DNA coding sequence and amino acid structure of Jak2 kinase is provided by the invention.

61. 5,721,237, Feb. 24, 1998, Protein tyrosine kinase aryl and heteroaryl quinazoline compounds having selective inhibition of HER-2 autoprophosphorylation properties; Michael R. Myers, et al., 514/259, 255; 544/283, 284, 287, 293 [IMAGE AVAILABLE]

US PAT NO: 5,721,237 [IMAGE AVAILABLE] L2: 61 of 92

**ABSTRACT:**  
This invention relates to a method for the selective treatment of cell growth and differentiation characterized by activity of the human epidermal growth factor receptor type 2 (HER2). More specifically, this invention relates to the use of substituted or unsubstituted mono- or bi-cyclic aryl, heteroaryl, cycloalkyl or heterocycloalkyl compounds in selectively regulating cell growth. Pharmaceutical compositions useful for the selective treatment of cell growth and differentiation are also described.

62. 5,714,493, Feb. 3, 1998, Aryl and heteroaryl quinazoline compounds which inhibit CSF-1R receptor tyrosine kinase; Michael R. Myers, et al., 514/259, 230.5, 248, 249, 252, 253, 254 [IMAGE AVAILABLE]

US PAT NO: 5,714,493 [IMAGE AVAILABLE] L2: 62 of 92

**ABSTRACT:**  
This invention relates to the treatment of intimation in a patient suffering from such disorder. More specifically, the invention relates to mono- and/or bicyclic aryl or heteroaryl quinazoline compounds in the treatment of inflammation.

63. 5,709,858, Jan. 20, 1998, Antibodies specific for Rse \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\*; Paul J. Godowski, et al., 424/143.1, 139.1; 435/7.4; 530/387.3, 387.9, 388.22, 391.1, 391.3 [IMAGE AVAILABLE]

US PAT NO: 5,709,858 [IMAGE AVAILABLE] L2: 63 of 92

**ABSTRACT:**  
The \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* \*\*receptors\*\*, designated Rse and HPTK6, have been purified from human and/or murine cell tissues. Rse and HPTK6 have been cloned from a cDNA library of a human liver carcinoma cell line (i.e., Hep 3B) using PCR amplification. Provided herein are nucleic acid sequences encoding Rse and HPTK6 useful as diagnostics and in the recombinant preparation of Rse and HPTK6. Rse and HPTK6 are used in the preparation and purification of antibodies thereto and in diagnostic assays.

64. 5,705,625, Jan. 6, 1998, Nucleic Acid Encoding novel protein tyrosine kinase; Curt I. Civin, et al., 536/23.5; 435/69.1, 194, 252.3, 254.11, 320.1, 325 [IMAGE AVAILABLE]

US PAT NO: 5,705,625 [IMAGE AVAILABLE] L2: 64 of 92

**ABSTRACT:**  
A novel protein tyrosine kinase, JAK3, and a polynucleotide sequence encoding JAK3 polypeptide are disclosed herein. JAK3 is a new member of the JAK family of protein tyrosine kinases which are important in regulation of cellular proliferation and differentiation. Also disclosed are therapeutic methods utilizing JAK3 polypeptide and polynucleotide sequences.

65. 5,693,488, Dec. 2, 1997, Transmembrane tyrosine phosphatase, nucleic acids encoding the same, and methods of use thereof; Kathy S. Fang, et al., 435/69.1, 196, 252.3, 320.1, 325, 348, 365; 536/23.2, 24.3 [IMAGE AVAILABLE]

US PAT NO: 5,693,488 [IMAGE AVAILABLE] L2: 65 of 92

**ABSTRACT:**  
The present invention relates to regulation and control of cellular processes by transmembrane protein tyrosine phosphatases, and to ligands that agonize or antagonize tyrosine phosphorylation mediated by such tyrosine phosphatases. This invention further relates to diagnosis and therapy based on the activity of such ligands. In particular, the invention provides a novel transmembrane protein tyrosine phosphatase-lambda (PTP.lambda.), nucleic acids encoding the same, antibodies to the PTP.lambda., and methods for identifying ligands to the PTP.lambda. of the invention. A specific Example describes the isolation and characterization of the first chicken transmembrane PTP, called ChPTP.lambda.. It has a unique extracellular domain containing a Ser/Thr/Pro-rich region, spectrin-like repeats, a fibronectin III domain, and an alternatively spliced N-terminus. The expression of ChPTP.lambda. in various tissues and cells was also examined. ChPTP.lambda. was shown to have a tyrosine-specific phosphatase activity, and the basic characteristics of this enzyme were studied.

66. 5,676,946, Oct. 14, 1997, Phospholipase C homolog; Phillip R. Hawkins, et al., 424/94.6; 435/69.1, 198, 252.33, 320.1; 536/23.2 [IMAGE AVAILABLE]

US PAT NO: 5,676,946 [IMAGE AVAILABLE] L2: 66 of 92

**ABSTRACT:**  
The present invention provides nucleotide and amino acid sequences that identify and encode a novel phospholipase C homolog (plch and PLCH). The present invention also provides for antisense molecules to the plch nucleotide sequences, expression vectors for the production of purified

PLCH, antibodies capable of binding specifically to PLCH, hybridization probes or oligonucleotides for detecting excess PLCH-encoding nucleotide sequences, genetically engineered host cells for the expression of PLCH, diagnostic tests for activated, inflamed, diseased, and hydroxyurea-resistant cells and/or tissues based on PLCH-encoding nucleic acid molecules and antibodies capable of binding specifically to PLCH.

67. 5,667,981, Sep. 16, 1997, Diagnostics and treatments for cancers expressing tyrosine phosphorylated CRKL protein; John H. Groffen, et al., 435/7.23, 7.24; 436/63, 64, 813 [IMAGE AVAILABLE]

US PAT NO: 5,667,981 [IMAGE AVAILABLE] L2: 67 of 92

**ABSTRACT:**  
The invention relates to methods and kits for diagnosing cancers arising from cells which express tyrosine phosphorylated CRKL protein, such as cells having the Philadelphia (Ph) chromosome, which includes chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL), through the detection of increased levels of phosphorylated CRKL protein or through the detection of increased CRKL gene copy or mRNA expression. The invention also relates to methods of treating such cancers.

68. 5,667,780, Sep. 16, 1997, Antibodies to SMDF; Wei-Hsien Ho, et al., 424/139.1; 530/387.3, 387.9, 388.23, 388.85, 389.2, 391.3 [IMAGE AVAILABLE]

US PAT NO: 5,667,780 [IMAGE AVAILABLE] L2: 68 of 92

**ABSTRACT:**  
Isolated SMDF, isolated DNA encoding SMDF, and antibodies to SMDF are disclosed. SMDF contains a beta-type EGF-like domain and a N-terminal sequence which is distinct from all neuregulins reported so far. SMDF, when expressed in recombinant cell culture, activates tyrosine phosphorylation of the HER2/neu receptor in human breast cancer cells and displays mitogenic activity on Schwann cells. Northern blot and *in situ* hybridization analysis show that SMDF differs from other neuregulins in that it is nervous tissue specific, and is very highly expressed, in comparison to other neuregulins, in the human and rat spinal cord motor neurons and sensory neurons.

69. 5,659,012, Aug. 19, 1997, Peptide which binds SH.sub.2 domains of protein tyrosine phosphatase SH-PTP1; Ursula Klingmuller, et al., 530/327, 300, 345, 350, 352, 399 [IMAGE AVAILABLE]

US PAT NO: 5,659,012 [IMAGE AVAILABLE] L2: 69 of 92

**ABSTRACT:**  
Novel assays for identifying agents which alter the effect of erythropoietin on proliferation of erythroid cells and agents identified thereby. Novel peptide comprising the erythropoietin receptor binding site for SH-PTP1.

70. 5,650,317, Jul. 22, 1997, Human breast epithelial cell type with stem cell and luminal epithelial cell characteristics; Chia-Cheng Chang, et al., 435/371, 378 [IMAGE AVAILABLE]

US PAT NO: 5,650,317 [IMAGE AVAILABLE] L2: 70 of 92

**ABSTRACT:**  
Described is a substantially purified human breast epithelial cell (Type I HBEC) displaying the following characteristics: variable cell shape; smooth cell colony boundary; deficiency in gap junctional

intercellular communication; positive expression of epithelial membrane antigen and keratin 18; negative expression of keratin 14, .alpha.6 integrin and gap junction genes for connexins (Cx26, Cx32 and Cx43); growth promotion by fetal bovine serum; induction by cholera toxin to differentiate into Type II HBEC (prior art); and acquisition of anchorage independent growth by Semliki virus 40 transfection. Also described is a method of obtaining the above-identified epithelial cells comprising the steps of: a) development of a mixture of human breast epithelial cells from reduction mammoplasty tissues using the MSU-1 medium; b) eliminating stromal fibroblasts by a trypsin (0.002%) and ethylenediamine tetraacetic acid (0.02%) solution; c) separating Type I HBEC from Type II HBEC which attach on culture dishes earlier by collecting Type I HBEC that remain in suspension after trypsinization and prolonged incubation; d) the continuing culture of these cells in MSU-1 medium supplemented with fetal bovine serum, which inhibits the growth of Type II HBEC while promoting the growth of Type I HBEC, gives rise to Type I HBEC. Described also is a new defined medium (the MSU-1 medium) which supports the growth of both Type I and Type II human breast epithelial cells.

71. 5,635,388, Jun. 3, 1997, Agonist antibodies against the flk2/flt3 receptor and uses thereof; Brian D. Bennett, et al., 435/334; 424/85.1, 85.2, 85.5; 435/70.21, 320.1, 328; 530/351, 387.3, 388.22, 389.1; 536/23.53 [IMAGE AVAILABLE]

US PAT NO: 5,635,388 [IMAGE AVAILABLE] L2: 71 of 92

**ABSTRACT:**  
Agonist antibodies are disclosed which bind to the extracellular domain of the flk2/flt3 receptor and thereby activate the intracellular kinase domain thereof. The labeled antibodies are useful as diagnostics for detecting the presence of the flk2/flt3 receptor in primitive hematopoietic cells for example. The antibodies are able to cause primitive hematopoietic cells to proliferate and/or differentiate and thereby enhance repopulation of mature blood cell lineages in a mammal which has undergone chemo- or radiation therapy or bone marrow transplantation. The antibodies are further useful for treating mammals which have suffered a decrease in blood cells as a consequence of disease or a hemorrhage, for example.

72. 5,635,177, Jun. 3, 1997, Protein tyrosine kinase agonist antibodies; Brian D. Bennett, et al., 424/143.1, 138.1, 146.1, 155.1; 435/330, 334, 338; 530/387.7, 388.26 [IMAGE AVAILABLE]

US PAT NO: 5,635,177 [IMAGE AVAILABLE] L2: 72 of 92

**ABSTRACT:**  
Agonist antibodies are disclosed which bind to the extracellular domain of \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* pTKs, and thereby cause dimerization and activation of the intracellular tyrosine kinase domain thereof. The antibodies are useful for activating their respective receptor and thereby enabling the role of the tyrosine kinase receptor in cell growth and/or differentiation to be studied. Chimeric proteins comprising the extracellular domain of the receptor pTKs and an immunoglobulin constant domain sequence are also disclosed.

73. 5,625,121, Apr. 29, 1997, Mice deficient in nerve growth factor

receptors encoded by trkB; Rudiger Klein, et al., 800/9; 435/325, 354 [IMAGE AVAILABLE]

US PAT NO: 5,625,121 [IMAGE AVAILABLE] L2: 73 of 92

**ABSTRACT:**  
The present invention provides mice and mouse cell lines having a homozygous or heterozygous deficiency in a gene encoding a neurotrophin receptor. In a preferred embodiment of this invention, mice and cell lines carry a trkB locus specifically targeted within its tyrosine protein kinase sequences. Mice homozygous for this mutation express gp95.sup.trkB receptor of unknown function but not the high affinity functional gp145.sup.trkB tyrosine protein kinase receptors. This mutation results in multiple CNS and PNS neuronal deficiencies and in a postembryonic lethal phenotype. Such genetically modified mice are useful in model systems for studying human diseases involving neuronal degeneration and neuronal cell loss, as well as in screening for genes, proteins, or other compounds that may prevent or impede neuronal cell death or stimulate neuronal regeneration.

74. 5,624,899, Apr. 29, 1997, Method for using Htk ligand; Brian D. Bennett, et al., 514/12, 2; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,624,899 [IMAGE AVAILABLE] L2: 74 of 92

**ABSTRACT:**  
A novel hepatoma transmembrane kinase receptor ligand (Htk ligand) which binds to, and activates, the Htk receptor is disclosed. As examples, mouse and human Htk ligands have been identified in a variety of tissues using a soluble Htk-Fc fusion protein. The ligands have been cloned and sequenced. The invention also relates to nucleic acids encoding the ligand, methods for production and use of the ligand, and antibodies directed thereto.

75. 5,621,090, Apr. 15, 1997, Nucleic acids encoding soluble human FLK-2 extracellular domain; Ihor R. Lemischka, 536/23.5; 435/69.1 [IMAGE AVAILABLE]

US PAT NO: 5,621,090 [IMAGE AVAILABLE] L2: 75 of 92

**ABSTRACT:**  
Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are provided. Also included are the receptors encoded by such nucleic acid molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1A (murine flk-2), FIG. 2, FIG. 1B (human flk-2) and FIG. 2 (murine flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1A, FIG. 1B and FIG. 2; ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the proliferation and/or differentiation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

76. 5,618,709, Apr. 8, 1997, Antisense oligonucleotides specific for

STK-1 and method for inhibiting expression of the STK-1 protein; Alan M. Gewirtz, et al., 435/375; 536/24.5 [IMAGE AVAILABLE]

US PAT NO: 5,618,709 [IMAGE AVAILABLE] L2: 76 of 92

**ABSTRACT:**  
Oligonucleotides are provided having a nucleotide sequence complementary to at least a portion of the mRNA transcript of the STK-1 gene. These "antisense" oligonucleotides are hybridizable to the STK-1 mRNA transcript. Such oligonucleotides are useful in treating neoplastic diseases characterized by activation of STK-1 gene expression. The oligonucleotides are also useful as bone marrow purging agents in the treatment of leukemia and metastasized neoplasms.

77. 5,614,642, Mar. 25, 1997, Methods of inhibiting phosphatase activity and treatment of disorders associated therewith using naphthopyrones and derivatives thereof, Peng C. Tang, et al., 549/389 [IMAGE AVAILABLE]

US PAT NO: 5,614,642 [IMAGE AVAILABLE] L2: 77 of 92

**ABSTRACT:**  
The present invention relates to organic molecules capable of inhibiting protein tyrosine phosphatase activity. The invention further relates to the use of such molecules to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity. Finally, the invention relates to the use of such molecules to treat various disease states including diabetes mellitus.

78. 5,602,171, Feb. 11, 1997, Methods of inhibiting phosphatase activity and treatment of disorders associated therewith using naphthopyrones and derivatives thereof, Peng C. Tang, et al., 514/455; 549/389 [IMAGE AVAILABLE]

US PAT NO: 5,602,171 [IMAGE AVAILABLE] L2: 78 of 92

**ABSTRACT:**  
The present invention relates to organic molecules capable of inhibiting protein tyrosine phosphatase activity. The invention further relates to the use of such molecules to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity. Finally, the invention relates to the use of such molecules to treat various disease states including diabetes mellitus.

79. 5,587,306, Dec. 24, 1996, Phospholipase C homolog; Phillip R. Hawkins, et al., 435/198, 252.33, 320.1; 536/23.2 [IMAGE AVAILABLE]

US PAT NO: 5,587,306 [IMAGE AVAILABLE] L2: 79 of 92

**ABSTRACT:**  
The present invention provides nucleotide and amino acid sequences that identify and encode a novel phospholipase C homolog (plch and PLCH). The present invention also provides for antisense molecules to the plch nucleotide sequences, expression vectors for the production of purified PLCH, antibodies capable of binding specifically to PLCH, hybridization probes or oligonucleotides for the detecting excess PLCH-encoding nucleotide sequences, genetically engineered host cells for the expression of PLCH, diagnostic tests for activated, inflamed, diseased, and hydroxyurea-resistant cells and/or tissues based on PLCH-encoding nucleic acid molecules and antibodies capable of binding specifically to

PLCH.

80. 5,571,894, Nov. 5, 1996, Recombinant antibodies specific for a growth factor receptor; Winfried S. Wels, et al., 530/387.3; 435/69.1; 530/350; 536/23.4 [IMAGE AVAILABLE]

US PAT NO: 5,571,894 [IMAGE AVAILABLE] L2: 80 of 92

**ABSTRACT:**

The invention concerns recombinant antibodies directed to the extracellular domain of the human growth factor receptor c-erbB-2 comprising a light chain variable domain and a heavy chain variable domain of a monoclonal antibody, monoclonal antibodies directed to c-erbB-2 themselves, a method of manufacturing those recombinant and monoclonal antibodies, hybridoma cells secreting those monoclonal antibodies, a method of manufacturing those hybridoma cells, DNAs encoding the heavy and light chain variable domains and the recombinant antibody, a method of manufacturing that DNA, hybrid vectors suitable for the expression of that DNA, host cells transformed with that DNA, and processes of using those recombinant and monoclonal antibodies in the diagnosis and treatment of tumors.

81. 5,548,065, Aug. 20, 1996, Tyrosine kinase receptor human flk-2-specific antibodies; Ihor R. Lemischka, 530/388.22, 387.9, 388.23, 388.7, 389.2, 389.6 [IMAGE AVAILABLE]

US PAT NO: 5,548,065 [IMAGE AVAILABLE] L2: 81 of 92

**ABSTRACT:**

Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are provided. Also included are the receptors encoded by such nucleic acid molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1a (murine flk-2), FIG. 1b (human flk-2) and FIG. 2 (murine flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1a, FIG. 1b and FIG. 2; ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the proliferation and/or differentiation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

82. 5,538,886, Jul. 23, 1996, Receptor-type phosphotyrosine phosphatase-alpha; Joseph Schlessinger, et al., 435/325, 6, 69.1, 69.8, 70.1, 71.2, 196, 252.3, 254.2, 320.1, 365; 536/23.1, 23.2 [IMAGE AVAILABLE]

US PAT NO: 5,538,886 [IMAGE AVAILABLE] L2: 82 of 92

**ABSTRACT:**

A novel receptor-type protein tyrosine phosphatase (RPTP) protein or glycoprotein and the DNA coding therefor is expressed in a wide variety of mammalian tissues. Included in this family of proteins are human RPTP.alpha., human RPTP.beta. and human RPTP.gamma.. The RPTP protein or glycoprotein may be produced by recombinant means. Antibodies to the proteins, methods for measuring the quantity of the proteins, methods for

screening compounds, such as drugs, which can bind to the proteins and inhibit or stimulate their activity, are provided.

83. 5,536,636, Jul. 16, 1996, Methods for identifying a tyrosine phosphatase abnormality associated with neoplastic disease; Robert M. Freeman, Jr., et al., 435/6, 91.1, 91.2; 536/24.3, 24.31 [IMAGE AVAILABLE]

US PAT NO: 5,536,636 [IMAGE AVAILABLE] L2: 83 of 92

**ABSTRACT:**

The present invention relates to the isolation of genes encoding novel protein tyrosine phosphatases (PTPs) having SH2 domains, the nucleic acid sequences isolated, and the encoded phosphatases. The invention further relates to methods of altering tyrosine phosphatase activities encoded by the novel phosphatases. By altering (i.e., increasing or decreasing) tyrosine phosphatase activity, one can alter megakaryocyte cell function, and thereby alter platelet production. Alteration of the genes is associated with neoplastic disease.

84. 5,521,295, May 28, 1996, Nucleic acids encoding hybrid receptor molecules; Robert E. Pacifici, et al., 536/23.4; 435/7.1, 320.1, 325, 354, 365, 372; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,521,295 [IMAGE AVAILABLE] L2: 84 of 92

**ABSTRACT:**

Provided are hybrid receptor molecules wherein one domain of the receptor is derived from the cytokine superfamily of receptors and other domain is derived from a heterologous family of receptors. Also provided are methods for identifying ligands that bind to the hybrid receptor molecules.

85. 5,476,851, Dec. 19, 1995, Pyrazolo[3,4-g]quinoxaline compounds which inhibit PDGF \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\*; Michael R. Myers, et al., 514/250; 544/345 [IMAGE AVAILABLE]

US PAT NO: 5,476,851 [IMAGE AVAILABLE] L2: 85 of 92

**ABSTRACT:**

This invention relates to pyrazolo[3,4-g]quinoxaline compounds exhibiting protein tyrosine kinase inhibition activity of the formula: ##STR1## where: ----- may be a double bond; R, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as described in claim 1; a pharmaceutically acceptable salt thereof. More specifically, compounds of this invention are novel as selective inhibitors of the PDGF-R protein tyrosine kinase and can be applied as potential therapeutic agents for various disease states which are characterized by uncontrolled cellular proliferation. Further, the present invention provides pharmaceutical compositions and a method for treating such disorders comprising the administration to a patient of a PDGF receptor inhibiting effective amount of a pyrazolo[3,4-g]quinoxaline compound exhibiting protein tyrosine kinase inhibition activity. Processes for the preparation of pyrazolo[3,4-g]quinoxaline compounds are also described.

86. 5,457,048, Oct. 10, 1995, Eph-related tyrosine kinases, nucleotide sequences and methods of use; Elena B. Pasquale, et al., 435/252.3, 194, 320.1; 536/23.2, 23.5 [IMAGE AVAILABLE]

US PAT NO: 5,457,048 [IMAGE AVAILABLE] L2: 86 of 92

**ABSTRACT:**

The invention is directed to substantially purified Eph-related protein tyrosine kinases, or functional fragments thereof, having about 23 to 66

percent amino acid sequence identity in their carboxyl terminal variable regions compared to known members of the Eph subclass of tyrosine kinases. Nucleic acids encoding such Eph-related protein tyrosine kinases, vectors and host cells are also provided. The invention is also directed to a method of diagnosing cancer and determining cancer prognosis. The method includes removing a tissue or cell sample from a subject suspected of having cancer and determining the level of Eph-related protein tyrosine kinase in the sample, wherein a change in the level or activity of a Eph-related protein tyrosine kinase compared to a normal sample indicates the presence of a cancer or indicates the level of malignancy of a cancer.

87. 5,447,860, Sep. 5, 1995, Tyrosine kinase; Steven F. Ziegler, 435/363, 194, 252.3, 254.11, 320.1; 536/23.2, 23.5 [IMAGE AVAILABLE]

US PAT NO: 5,447,860 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**  
A novel \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* named ork (orphan receptor tyrosine kinase) is identified and characterized. cDNA encoding the ork protein is inserted into an expression vector for production of the protein via recombinant DNA technology. The ork cDNA, when transfected into Cos-7 cells, encodes a 140 Kd protein with in vitro kinase activity. The ork gene is expressed predominantly in placenta and lung, with lower levels in umbilical vein endothelial cells, brain and kidney.

88. 5,367,057, Nov. 22, 1994, Tyrosine kinase receptor flk-2 and fragments thereof; Ihor R. Lemischka, 530/350, 403 [IMAGE AVAILABLE]

US PAT NO: 5,367,057 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**  
Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are provided. Also included are the receptors encoded by such nucleic acid molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1 (murine flk-2), FIG. 2 (human flk-2) and FIG. 3 (murine flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1 (murine flk-2), FIG. 2 (human flk-2) and FIG. 3; ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the proliferation and/or differentiation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

89. 5,283,354, Feb. 1, 1994, Nucleic acids encoding hematopoietic stem cells receptors flk-1; Ihor R. Lemischka, 536/23.5; 435/69.1; 530/350, 403 [IMAGE AVAILABLE]

US PAT NO: 5,283,354 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**  
Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are

provided. Also included are the receptors encoded by such nucleic acid molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1(flk-2) and FIG. 2 (flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1(flk-2) and FIG. 2 (flk-1); ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the proliferation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

90. 5,270,458, Dec. 14, 1993, Nucleic acids encoding fragments of hematopoietic stem cell receptor flk-2; Ihor R. Lemischka, 536/23.5; 435/69.1, 320.1; 530/350, 403 [IMAGE AVAILABLE]

US PAT NO: 5,270,458 [IMAGE AVAILABLE] L2:  
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**ABSTRACT:**  
Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are provided. Also included are the receptors encoded by such nucleic acid molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1a (murine flk-2), FIG. 1b (human flk-2) and FIG. 2 (murine flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1a, FIG. 1b and FIG. 2; ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the proliferation and/or differentiation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

91. 5,217,999, Jun. 8, 1993, Styryl compounds which inhibit EGFR \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\*; Alexander Levitzki, et al., 514/613 [IMAGE AVAILABLE]

US PAT NO: 5,217,999 [IMAGE AVAILABLE] L2:  
91 of 92

**ABSTRACT:**  
A method of inhibiting cell proliferation in a patient suffering from such disorder comprising administering to said patient an effective amount of a composition comprising, in admixture with a pharmaceutically acceptable carrier, a compound, or a pharmaceutically acceptable salt thereof, which is a substituted styrene compound which can also be a naphthalene, an indane or a benzoxazine; including nitrile and molononitrile compounds, and pharmaceutical compositions comprising, in admixture with a pharmaceutically acceptable carrier, a pharmaceutically-effective amount of such compound.

92. 5,185,438, Feb. 9, 1993, Nucleic acids encoding hematopoietic stem cell receptor flk-2; Ihor R. Lemischka, 536/23.2; 435/69.1, 320.1; 530/350, 403 [IMAGE AVAILABLE]

US PAT NO: 5,185,438 [IMAGE AVAILABLE] L2:  
92 of 92

**ABSTRACT:**  
Isolated mammalian nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* expressed in primitive hematopoietic cells and not expressed in mature hematopoietic cells are provided. Also included are the receptors encoded by such nucleic acid molecules; the nucleic acid molecules encoding \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the sequences shown in FIG. 1 (flk-2) and FIG. 2 (flk-1); the \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinases\*\* having the amino acid sequences shown in FIG. 1 (flk-2) and FIG. 2 (flk-1); ligands for the receptors; nucleic acid sequences that encode the ligands; and methods of stimulating the proliferation of primitive mammalian hematopoietic stem cells comprising contacting the stem cells with a ligand that binds to a \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\* expressed in primitive mammalian hematopoietic cells and not expressed in mature hematopoietic cells.

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| 1933 RET                           |
| 0 ORPHAN C-RET                     |
| (ORPHAN(W)C(W)RET)                 |
| 309 ORPHAN                         |
| 1373455 C                          |
| 1933 RET                           |
| 0 ORPHAN C RET                     |
| (ORPHAN(W)C(W)RET)                 |
| L10 0 ORPHAN C-RET OR ORPHAN C RET |

=> d his

(FILE 'USPAT ENTERED AT 16:05:05 ON 05 OCT 1999)  
E CLARY, DOUGLAS/TN

|  |
|--|
| L1 1 S E4                                  |
| L2 92 S PROTEIN TYROSINE KINASE RECEPTOR/# |
| OR RECEPTOR PROTEIN TY                     |
| ROS  |
| L3 3 S L2 AND RET                          |
| L4 1934 S L1 AND EPIDERMAL GROWTH FACTOR   |
| RECEPTOR/# OR RET                          |
| L5 1 S L1 AND (EPIDERMAL GROWTH FACTOR     |
| RECEPTOR/# OR RET)                         |
| L6 3 S L3 AND (EPIDERMAL GROWTH FACTOR     |
| RECEPTOR/# OR RET)                         |
| L7 0 S L3 AND (C-RET OR C RET)             |
| L8 24 S C-RET OR C RET                     |
| L9 10 S L8 AND RECEPTOR/#                  |
| L10 0 S ORPHAN C-RET OR ORPHAN C RET       |

=> d l3 cit kwic 1-3

1. 5,942,428, Aug. 24, 1999, Crystals of the tyrosine kinase domain of non-insulin receptor tyrosine kinases; Moosa Mohammadi, et al., 435/194, 69.1; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,942,428 [IMAGE AVAILABLE] L3:  
1 of 3

DRAWING DESC:

DRWD(7)

FIGS. . . . EPH [SEQ ID NO: 23], RYK [SEQ ID NO: 24], DDR [SEQ ID NO: 25], ROS [SEQ ID NO: 26], \*\*RET\*\* [SEQ ID NO: 27], LTK [SEQ ID NO: 28], ROR1 [SEQ ID NO: 29], and MUSK [SEQ ID NO: 30]. . .

DETDESC:

DETD(198)  
Taylor et al., 1995, "How do protein kinases discriminate between serine/threonine and tyrosine? Structural insights from the insulin \*\*receptor\*\* \*\*protein\*\* \*\*tyrosine\*\* \*\*kinase\*\*", FASEB Journal 9(12):1255-66.

DETDESC:

DETD(202)  
van der Geer et al., 1994, "Receptor\*\*  
\*\*protein\*\*-tyrosine\*\*  
\*\*kinases\*\* and their signal transduction pathways," Annu.  
Rev. Cell  
Biol. 10:251-337.

2. 5,734,039, Mar. 31, 1998, Antisense oligonucleotides  
targeting  
cooperating oncogenes; Bruno Calabretta, et al., 536/24.5  
[IMAGE  
AVAILABLE]

US PAT NO: 5,734,039 [IMAGE AVAILABLE] L3:  
2 of 3

SUMMARY:

BSUM(5)

carcinoma of thyroid  
N-ras Carcinoma of genitourinary  
Point muta-  
tract and thyroid; melano-  
ma; leukemia  
\*\*ret\*\* Carcinoma of thyroid  
Rearrange-  
ment  
ros Astrocytoma ?  
K-sam Carcinoma of stomach  
Amplifica-  
tion  
sis Astrocytoma . . .

SUMMARY:

BSUM(40)

The . . . can be vehicles for transformation by disturbances  
elsewhere in signalling pathways, e.g., constitutive production  
of  
growth factors that act through \*\*protein\*\*-tyrosine\*\*  
\*\*kinase\*\*  
\*\*receptors\*\* (Aaronson & Pierce, Cancer Cells 2, 212-214,  
1990) and the  
effects of phosphatases, which play crucial roles in governing  
the  
activity. . .

3. 5,447,860, Sep. 5, 1995, Tyrosine kinase; Steven F. Ziegler,  
435/363,  
194, 252.3, 254.11, 320.1; 536/23.2, 23.5 [IMAGE  
AVAILABLE]

US PAT NO: 5,447,860 [IMAGE AVAILABLE] L3:  
3 of 3

ABSTRACT:

A novel \*\*receptor\*\*-protein\*\*-tyrosine\*\*-kinase\*\*  
named ork  
(orphan receptor tyrosine kinase) is identified and  
characterized. cDNA  
encoding the ork protein is inserted into an expression. . .

DETDESC:

DETD(2)

The present invention provides a novel \*\*receptor\*\*-  
\*\*protein\*\*-  
\*\*tyrosine\*\*-kinase\*\*, isolated DNA encoding the tyrosine  
kinase,  
recombinant expression vectors containing the isolated DNA,  
and host  
cells transformed with the recombinant. . .

DETDESC:

DETD(5)

Using a polymerase chain reaction-based approach we have  
isolated ork  
cDNA and characterized this novel \*\*receptor\*\*-protein\*\*-  
\*\*tyrosine\*\*-  
\*\*kinase\*\*. As described in example 1 below, degenerate  
oligonucleotide  
probes based on certain sequences that are conserved within  
the kinase  
domain. . .

DETDESC:

DETD(11)

A . . . the two parts of the kinase domains (FIG. 1). This  
insert is  
similar in size to that seen in the \*\*ret\*\* gene (Takahashi and  
Cooper,  
Mol. Cell. Biol. 7:1378-1385, 1987). However, unlike the insert  
sequences  
in other RTK subgroups, the insert. . .

=> d 11 cit kwic

1. 5,753,225, May 19, 1998, Antibodies that mimic actions of  
neurotrophins; \*\*Douglas O. Clary\*\*, et al., 424/130.1, 141.1,  
143.1,  
156.1; 530/387.1, 388.1, 388.22 [IMAGE AVAILABLE]

US PAT NO: 5,753,225 [IMAGE AVAILABLE] L1:  
1 of 1

INVENTOR: \*\*Douglas O. Clary\*\*, San Francisco, CA  
Gisela Weskamp, New York, NY  
Leann R. Austin, San Francisco, CA  
Louis F. Reichardt, San Francisco, CA

=> d 15 cit kwic

1. 5,753,225, May 19, 1998, Antibodies that mimic actions of  
neurotrophins; \*\*Douglas O. Clary\*\*, et al., 424/130.1, 141.1,  
143.1,  
156.1; 530/387.1, 388.1, 388.22 [IMAGE AVAILABLE]

US PAT NO: 5,753,225 [IMAGE AVAILABLE] L5:  
1 of 1

INVENTOR: \*\*Douglas O. Clary\*\*, San Francisco, CA  
Gisela Weskamp, New York, NY  
Leann R. Austin, San Francisco, CA  
Louis F. Reichardt, San Francisco, CA

DETDESC:

DETD(3)

The . . . the amino acid tyrosine. The tyrosine kinases are  
tightly  
regulated in animal cells. One fairly well characterized tyrosine  
kinase  
is \*\*epidermal\*\*-growth\*\*-factor\*\*-receptor\*\* which  
assists in  
initiating cell division by phosphorylating key proteins. For  
information  
about the protein kinase families and hallmarks of. . .

=> d 19 cit kwic 1-10

1. 5,910,426, Jun. 8, 1999, Protein tyrosine kinase; Andrew  
Frederick  
Wilks, et al., 435/68.1; 530/402 [IMAGE AVAILABLE]

US PAT NO: 5,910,426 [IMAGE AVAILABLE] L9:  
1 of 10

SUMMARY:

BSUM(2)

Protein tyrosine kinases (PTKs) are structurally well suited to a  
role  
intracellular signal transduction. Many growth factor  
\*\*receptors\*\*, for  
example, transduce the extracellular stimulus they receive  
through  
interaction with their cognate ligand via an intracellular tyrosine  
kinase domain. At least one of the non-\*\*receptor\*\* PTKs,  
namely LCK, is  
believed to mediate the transduction in T-cells of a signal from the  
interaction of a cell-surface. . .

SUMMARY:

BSUM(3)

The . . . this family can be employed in a variety of cellular  
contexts. Similar PTK structural sub-families exist based  
around the FGF  
\*\*receptor\*\* and the CSF-1 \*\*receptor\*\* (reviewed in Wilks,  
1990).

DRAWING DESC:

DRWD(15)

FIG. . . of structural similarity, branch length a function of  
sequence identity. The abbreviations used are: SRC=c-src;  
YES=c-Yes;

FES=c-fes; CSF-1=R=Colony stimulatin factor-1 \*\*receptor\*\*;  
KIT=c-kit;  
PDGF-R=Platelet derived growth factor \*\*receptor\*\*-A;  
RET=\*\*c\*\*-\*\*RET\*\*;  
ANP-A=Atrial natriuretic peptide \*\*receptor\*\*-A;  
ANP-B=Atrial natriuretic  
peptide \*\*receptor\*\*-B; MOS=c-mos; PBS2=polyxin B  
antibiotic resistance  
gene product; STE7=sterile mutant wild-type allele gene  
product;  
JAK1/l=Domain-1 of Human JAK1; JAK1/2=PTK domain of

DETDESC:

DETD(30)

The . . . 1988) and the phospholipase-C family of proteins  
(Sub et al  
1988). This is a particularly interesting observation since no  
other  
non-\*\*receptor\*\* PTK has been described which lacks this  
feature. A  
hydrophilicity plot failed to demonstrate the present of a  
hydrophobic  
domain characteristic of the growth factor \*\*receptor\*\* type  
of PTK (FIG.  
3b) suggesting that this protein is wholly intracellular like other  
members of the non-\*\*receptor\*\* class of PTKs. The one  
outstanding  
feature of the JAK1 hydrophathy plot is the highly hydrophilic  
sequence  
between residues 320-350. . .

DETDESC:

DETD(37)

The . . . which pre-dated the development of the PTK  
sub-family. It  
is of interest to note that the kinase-related domains of the  
ANP-\*\*receptor\*\*/guanylate cyclase family diverge at a point  
close by.

2. 5,882,923, Mar. 16, 1999, Glial cell line-derived neurotrophic  
factor  
regulation of ureteric budding and growth; Hannu Sariola, et  
al.,  
435/325, 368, 369, 375, 384; 514/2 [IMAGE AVAILABLE]

US PAT NO: 5,882,923 [IMAGE AVAILABLE] L9:  
2 of 10

SUMMARY:

BSUM(8)

One known \*\*receptor\*\* for GDNF is the cRet \*\*receptor\*\*  
tyrosine kinase  
(Takahashi et al., 1988; Trupp et al., 1996; Durbec et al., 1996),  
which  
is expressed in several tissues adjacent to sites of GDNF  
synthesis and  
it is autoposphorylated upon GDNF binding. The functional  
\*\*receptor\*\*  
complex of GDNF and cRet additionally includes novel type of  
glycosylphosphatidylinositol-lined (GPI) cell surface  
\*\*receptors\*\*,  
GDNFR-alpha. (Jing et al., 1996; Treanor et al., 1996) or  
GDNFR-beta.  
(Suvanto et al., 1997; also named TGF-.beta.-related  
neurotrophic factor  
\*\*receptor\*\*\*, TimR2; Baloh et al., 1997). Comparative analysis  
of  
GDNFR-alpha., GDNFR-beta. and cRet expression suggests  
that multiple  
\*\*receptor\*\* complexes exist in vivo (Baloh et al. 1997,  
Suvanto et al., 1997). The ligand specificities of GDNFR-alpha. and  
GDNFR-beta. have  
. . . fully resolved, but they bind both GDNF and its novel  
homologue  
neurturin (Kotzbauer et al. 1996), and both these GPI-linked  
\*\*receptors\*\* can mediate growth factor signaling via cRet  
(Baloh et al., 1997).

DRAWING DESC:

DRWD(2)

FIGS. 1A-H. cRNA in situ hybridization of GDNF and GDNF  
\*\*receptor\*\*  
mRNAs and GDNF binding to the E.sub.r 17 metanephric  
kidney. A. cRet  
transcripts are seen only in the tips of. . .

DETDESC:

DETD(5)

In . . . tips of the ureteric epithelium, where the branches of the collecting ducts are continuously being formed. Although one of its \*\*receptors\*\*, the GPI-linked protein GDNFR-alpha. (Jung et al, 1996; Treanor et al., 1996), is expressed in both metanephric mesenchyme and ureric bud, we could only verify GDNF binding to the tips of the ureric branches where the cRet \*\*receptor\*\* tyrosine kinase is expressed. Furthermore, metanephric kidneys of mice deficient for cRet (Schuchardt et al., 1994, 1996) did not respond. . .

DETDESC:

DETD(8)

Competence . . . is that the mesenchymes lack effectors, so far unidentified, for bud elongation. These molecules may not represent the GPI-linked GDNF \*\*receptors\*\*, because all mesenchymes tested in the recombination assays express either GDNFR.alpha. or GDNFR.beta. (Treanor et al. 1996, Baloh et al. . . .

DETDESC:

DETD(12)

Activation of the cRet \*\*receptor\*\* tyrosine kinase is mitogenic for some cells (Santoro et al, 1994). In neuroblastoma cell lines, for example, cRet utilizes the . . .

DETDESC:

DETD(13)

There . . . has been associated to tracheal and Malpighian tubule formation (Eimeria et al., 1996). Drosophila fibroblast growth factor (DFGF) and its \*\*receptor\*\* breathless (Reichman-Fried and Shilo, 1995) as well as a TGF beta superfamily member decapentaplegic (Affolter et al., 1994), guide the migration. . .

DETDESC:

DETD(17)

Agarose . . . not observed in explants ret.k homozygous embryos, suggesting that the lack of response is exclusively due to the absence of \*\*c\*\*\*-\*\*ret\*\*\* \*\*receptor\*\* tyrosine kinase, and that normal \*\*c\*\*\*-\*\*ret\*\* functioning is necessary for GDNF signaling in the peripheral nervous system.

DETDESC:

DETD(40)

We . . . NO:2]. The identity of the cloned fragment was verified by direct sequencing with a Pharmacia A.L.F. automatic DNA sequencer. The \*\*c\*\*\*-\*\*ret\*\*\* probe spanned the tyrosine kinase domain of mouse \*\*c\*\*\*-\*\*ret\*\* (nucleotides 2534-3217; Pachnis et al., 1993). The cloning of rat GDNF probe for *in situ* hybridisation has been described in . . .

DETDESC:

DETD(43)

The . . . but was not expressed by the nephrogenic mesenchyme or by its derivatives as reported by Liu et al. (1996). The alpha-\*\*receptor\*\* (FIGS. 1C,D) showed an expression pattern that overlapped both GDNF (FIGS. 1 E, F; see also Hellmich et al.,

1996; . . .

DETDESC:

DETD(76)  
Affolter, M., Nellen, D., Nussbaumer, U. and Basle, K. (1994). Multiple requirements for the \*\*receptor\*\* serine/threonine kinase thick veins reveal novel functions of TGF-beta homologs during Drosophila embryogenesis. *Development* 120, 3105-3107

DETDESC:

DETD(78)  
Baloh, . . . Keck, C. L., Zimonjic D. B., Popescu, N. C., Johnson Jr., E. M. and Milbrandt, J. (1997). TrnR2, a novel \*\*receptor\*\* that mediated neuritin and GDNF signaling through ret. *Neuron* 18, 793-802.

DETDESC:

DETD(82)  
Durbec, . . . P., Smith, D., Ponder, B., Costantini, F., Saarma, M., Sariola, H. and Pachnis, V. (1996). GDNF signalling through the Ret \*\*receptor\*\* tyrosine kinase. *Nature (London)* 381, 789-793.

DETDESC:

DETD(90)  
Jing, . . . Hu, Cupples, R. et al (1996). GDNF-induced activation of the Ret protein tyrosine kinase is mediated by GDNFR-a, a novel \*\*receptor\*\* for GDNF. *Cell* 85, 9-20.

DETDESC:

DETD(95)  
Liu, . . . A., Carone, F. A., Takahashi, M. and Kanwar Y. S. (1996). Comparative role of phosphotyrosine kinase domains of c-ros and \*\*c\*\*\*-\*\*ret\*\* protooncogenes in metanephric development with respect to growth factors and matrix morphogens. *Devel. Biol.* 178, 133-148.

DETDESC:

DETD(107)  
Reichman-Fried, M. and Shilo B. Z. (1995). Breathless, a Drosophila FGF \*\*receptor\*\* homolog, is required for the onset of tracheal cell migration and tracheole formation. *Mech. Devel.* 52, 265-273.

DETDESC:

DETD(113)  
Santoro, . . . Aroca, P., Santos, E., Matoskova, B., Grieco, M., Fusco, A. and di Fiore, P. P. (1994). An epidermal growth factor \*\*receptor\*\*/ret chimera generates mitogenic and transforming signals: evidence for a ret-specific signaling pathway. *Molec. Cell. Biol.* 14, 663-675.

DETDESC:

DETD(120)  
Schuchardt, . . . Constantini, F. and Pachnis, V. (1994). Defects in the kidney and enteric nervous system of mice lacking the tyrosine kinase \*\*receptor\*\* Ret. *Nature (London)* 367, 380-383.

DETDESC:

DETD(124)  
Suvanto, . . . H. and Saarma M. (1997) Cloning, mRNA distribution and chromosomal localization of the gene for glial cell line-derived neurotrophic factor \*\*receptor\*\* beta, a homologue to GDNFR-alpha. *Hum. Mol. Gen.* 6, in press.

DETDESC:

DETD(129)

Treanor, . . . Beck, C. D., Gray, C., Armanini, M. P. Pollock, R. A., Hefti, F. et al. (1996). Characterization of a multicomponent \*\*receptor\*\* for GDNF. *Nature (London)* 382, 80-83.

DETDESC:

DETD(130)  
Trupp, . . . Nilsson, A. -S., Sieber, B. -A., Grigoriou, M., Kilkenney, C., Salazar-Grueso, E., Pachnis, V., Arumac, U. et al. (1996). Functional \*\*receptor\*\* for GDNF encoded by the cRet proto-oncogene. *Nature (London)* 381, 785-789.

DETDESC:

DETD(133)  
Vega, . . . C. A., Lechner, M. S. Dixon, J. E. and Dressler, G. R. (1996). Glial cell line-derived neurotrophic factor activates the \*\*receptor\*\* tyrosine kinase ret and promotes kidney morphogenesis. *Proc. Natl. Acad. Sci. (USA)* 93, 10657-10661.

DETDESC:

DETD(137)  
Woolf, . . . G., Jat, P. S. Noble, M. D. and Gherardi, E. (1995). Roles of hepatocyte growth factor/scatter factor and the met \*\*receptor\*\* in the early development of the metanephros. *J. Cell Biol.* 128, 171-184.

DETDESC:

DETD(138)  
Worby, . . . H. H. -J., Seasholtz, A. F. and Dixon, J. E. (1996). Glial cell line-derived neurotrophic factor signals through the RET \*\*receptor\*\* and activates mitogen-activated protein kinase. *J. Biol. Chem.* 271, 23619-23622.

3. 5,852,184, Dec. 22, 1998, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 536/23.4; 435/194, 320.1; 536/23.1 [IMAGE AVAILABLE]

US PAT NO: 5,852,184 [IMAGE AVAILABLE] L9: 3 of 10

SUMMARY:

BSUM(2)

Protein tyrosine kinases (PTKs) are structurally well suited to a role intracellular signal transduction. Many growth factor \*\*receptors\*\*, for example, transduce the extracellular stimulus they receive through interaction with their cognate ligand via an intracellular tyrosine kinase domain. At least one of the non-\*\*receptor\*\* PTKs, namely LCK, is believed to mediate the transduction in T-cells of a signal from the interaction of a cell-surface. . .

SUMMARY:

BSUM(3)

The . . . this family can be employed in a variety of cellular contexts. Similarly PTK structural sub-families exist based around the PGF \*\*receptor\*\* and the CSF-1 \*\*receptor\*\* (reviewed in Wilks, 1990).

SUMMARY:

BSUM(42)

FIG. . . . of structural similarity, branch length a function of sequence identity. The abbreviations used are: SRC=c-scr; YES=c-Yes; FES=c-fes; CSF1-R=Colony stimulating factor-1 \*\*receptor\*\*; KIT=c-kit; PDGF-R=Platelet derived growth factor \*\*receptor\*\*-A; RET=\*\*c\*\*\*-\*\*RET\*\*; ANP-B=Atrial natriuretic peptide \*\*receptor\*\*-A; ANP-A=Atrial natriuretic peptide \*\*receptor\*\*-B; MOS=c-mos; PBS2=polyxinn B antibiotic resistance gene product; STE7=steine mutant wild-type allele gene product;

JAK1/l=Domain-1 of Human JAK1; JAK1/2=PTK domain of

DETDESC:

DETD(30)

The . . . 1988) and the phospholipase-C family of proteins (Suh et al, 1988). This is a particularly interesting observation since no other non-\*\*receptor\*\* PTK has been described which lacks this feature. A hydrophilicity plot failed to demonstrate the present of a hydrophobic domain characteristic of the growth factor \*\*receptor\*\* type of PTK (FIG. 3b) suggesting that this protein is wholly intracellular like other members of the non-\*\*receptor\*\* class of PTKs. The one outstanding feature of the JAK1 hydropathy plot is the highly hydrophilic sequence between residues 320-350. . .

DETDESC:

DETD(37)

The . . . pre-dated the development of the PTK sub-family. It is of interest to note that the kinase related domains of the ANP-\*\*receptor\*\*/guanylate cyclase family diverge at a point close by.

4. 5,821,069, Oct. 13, 1998, Method for determining tyrosine kinase in a sample; Andrew Frederick Wilks, et al., 435/7.21; 530/387.9, 388.1, 388.25, 388.26, 388.85, 389.1 [IMAGE AVAILABLE]

US PAT NO: 5,821,069 [IMAGE AVAILABLE] L9:  
4 of 10

SUMMARY:

BSUM(2)

Protein tyrosine kinases (PTKs) are structurally well suited to a role intracellular signal transduction. Many growth factor \*\*receptors\*\*, for example, transduce the extracellular stimulus they receive through interaction with their cognate ligand via an intracellular tyrosine kinase domain. At least one of the non-\*\*receptor\*\* PTKs, namely LCK, is believed to mediate the transduction in T-cells of a signal from the interaction of a cell-surface. . .

SUMMARY:

BSUM(3)

The . . . this family can be employed in a variety of cellular contexts. Similar PTK structural sub-families exist based around the FGF \*\*receptor\*\* and the CSF-1 \*\*receptor\*\* (reviewed in Wilks, 1990).

DRAWING DESC:

DRWD(15)

FIG. . . length a function of sequence identity. The abbreviations used are: SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R= Colony stimulating factor-1 \*\*receptor\*\*; KIT=c-kit; PDGF-R= Platelet derived growth factor \*\*receptor\*\*-A; RET= \*\*c\*\*\*-\*\*RET\*\*; ANP-A= Atrial natriotic peptide \*\*receptor\*\*-A; ANP-B= Atrial natriotic peptide \*\*receptor\*\*-B; MOS=c-mos; PBS2=polyxin B antibiotic resistance gene product; STE7=sterile mutant wild-type allele gene product; JAK1= Domain-1 of Human JAK1;. . .

DETDESC:

DETD(30)

The . . . 1988) and the phospholipase-C family of proteins (Suh et al, 1988). This is a particularly interesting observation since no

other non-\*\*receptor\*\* PTK has been described which lacks this feature. A hydrophilicity plot failed to demonstrate the present of a hydrophobic domain characteristic of the growth factor \*\*receptor\*\* type of PTK (FIG. 3b) suggesting that this protein is wholly intracellular like other members of the non-\*\*receptor\*\* class of PTKs. The one outstanding feature of the JAK1 hydropathy plot is the highly hydrophilic sequence between residues 320-350. . .

DETDESC:

DETD(37)

The . . . which pre-dated the development of the PTK sub-family. It is of interest to note that the kinase-related domains of the ANP-\*\*receptor\*\*/guanylate cyclase family diverge at a point close by.

5. 5,808,036, Sep. 15, 1998, Stem-loop oligonucleotides containing parallel and antiparallel binding domains; Eric T. Kool, 536/24.3; 435/6, 320.1, 325, 375, 536/23.1, 24.5 [IMAGE AVAILABLE]

US PAT NO: 5,808,036 [IMAGE AVAILABLE] L9:  
5 of 10

DETDESC:

DETD(79)

Other ligands for cellular \*\*receptors\*\* may also have utility for improving cellular uptake, including, e.g. insulin, transferrin and others. Similarly, derivatization of oligonucleotides with poly-L-lysine. . .

DETDESC:

DETD(118)

Moreover, . . . c-ets, c-fgf, c-fms, c-fos, c-has/bas, her-2 neu, c-int, c-jun, c-kit, c-mas, c-met, c-mos, c-myb, c-myc, N-myc, p53, ras, c-Ha-ras, c-rel, \*\*c\*\*\*-\*\*ret\*\*\*, c-ros, c-sec, c-sis, c-ski, c-snoA, c-snoN, c-spi, c-src, c-syn, c-trk, c-vav and c-yes.

CLAIMS:

CLMS(14)

14. The oligonucleotide of claim 1 wherein said oligonucleotide is a conjugated oligonucleotide further comprising at least one of a cellular \*\*receptor\*\*, cholesterol group, an aryl group, a steroid group or a polycation.

6. 5,716,818, Feb. 10, 1998, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 435/194; 530/326, 328, 329, 350 [IMAGE AVAILABLE]

US PAT NO: 5,716,818 [IMAGE AVAILABLE] L9:  
6 of 10

SUMMARY:

BSUM(2)

Protein tyrosine kinases (PTKs) are structurally well suited to a role intracellular signal transduction. Many growth factor \*\*receptors\*\*, for example, transduce the extracellular stimulus they receive through interaction with their cognate ligand via an intracellular tyrosine kinase domain. At least one of the non-\*\*receptor\*\* PTKs, namely LCK, is believed to mediate the transduction in T-cells of a signal from the interaction of a cell-surface. . .

SUMMARY:

BSUM(3)

The . . . this family can be employed in a variety of cellular

contexts. Similar PTK structural sub-families exist based around the FGF \*\*receptor\*\* and the CSF-1 \*\*receptor\*\* (reviewed in Wilks, 1990).

DRAWING DESC:

DRWD(14)

FIG. . . of structural similarity, branch length a function of sequence identity. The abbreviations used are: SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R=Colony stimulating factor-1 \*\*receptor\*\*; KIT=c-kit; PDGF-R=Platelet derived growth factor \*\*receptor\*\*-A; RET=\*\*c\*\*\*-\*\*RET\*\*; ANP-A=Atrial natriotic peptide \*\*receptor\*\*-A; ANP-B=Atrial natriotic peptide \*\*receptor\*\*-B; MOS=c-mos; PBS2=polyxin B antibiotic resistance gene product; STE7=sterile mutant wild-type allele gene product; JAK1/l=Domain-1 of Human JAK1; JAK1/2=PTK domain of

DETDESC:

DETD(30)

The . . . 1988) and the phospholipase-C family of proteins (Suh et al, 1988). This is a particularly interesting observation since no other non-\*\*receptor\*\* PTK has been described which lacks this feature. A hydrophilicity plot failed to demonstrate the present of a hydrophobic domain characteristic of the growth factor \*\*receptor\*\* type of PTK (FIG. 3b) suggesting that this protein is wholly intracellular like other members of the non-\*\*receptor\*\* class of PTKs. The one outstanding feature of the JAK1 hydropathy plot is the highly hydrophilic sequence between residues 320-350. . .

DETDESC:

DETD(79)

The . . . which pre-dated the development of the PTK sub-family. It is of interest to note that the kinase-related domains of the ANP-\*\*receptor\*\*/guanylate cyclase family diverge at a point close by.

7. 5,681,714, Oct. 28, 1997, Nucleic acid encoding tek \*\*receptor\*\* tyrosine kinase; Martin L. Breitman, deceased, et al., 435/69.1, 194, 252.3, 254.11, 320.1, 325, 352, 358, 365, 367 [IMAGE AVAILABLE]

US PAT NO: 5,681,714 [IMAGE AVAILABLE] L9:  
7 of 10  
TITLE: Nucleic acid encoding tek \*\*receptor\*\* tyrosine kinase

ABSTRACT:  
Novel \*\*receptor\*\* tyrosine kinase protein and isoforms thereof which are expressed in cells of the endothelial lineage, and DNA segments encoding the novel protein and isoforms thereof are disclosed. Methods for identifying ligands which are capable of binding to the \*\*receptor\*\* protein and methods for screening for agonist or antagonist substances of the interaction of the protein and a ligand are. . .

SUMMARY:

BSUM(2)

The invention relates to a novel \*\*receptor\*\* tyrosine kinase protein, isoforms and parts thereof, nucleic acid molecules encoding the novel protein and fragments thereof, and uses of. . .

SUMMARY:

BSUM(4)

Transmembrane \*\*receptor\*\* tyrosine kinases (RTKs) comprise a large and

evolutionarily conserved family of structurally related proteins capable of transducing extracellular signals to . . .

SUMMARY:

BSUM(5)

In . . . 335, 88-89) and SI (Russell, E. S. (1979), Adv. Genet., 28, 357-459) loci have revealed the importance of the Kit \*\*receptor\*\* and its ligand in melanogenesis, hematopoiesis, and gametogenesis (Dubreuil, P., Rottapel, R., Reith, A. D., Forrester, L. & Bernstein, A. . . together with others (reviewed in Pawson, T. & Bernstein, A. (1991), Trends Gert., 6, 350-356), have established the importance of \*\*receptor\*\*-ligand interactions in the regulation of development.

SUMMARY:

BSUM(6)

Angiogenesis . . . Physiol., 53, 217-239, for reviews). However, many of these factors also show similar effects on other cell types, implying that \*\*receptors\*\* for these factors are also expressed by such cells.

SUMMARY:

BSUM(9)

The present inventors have identified and characterized a \*\*receptor\*\* tyrosine kinase protein that plays a critical role in murine cardiogenesis. The heart forms early in mouse embryogenesis and its . . .

SUMMARY:

BSUM(11)

The present inventors have cloned and sequenced a 4.2-kb murine cDNA encoding the novel \*\*receptor\*\* tyrosine kinase. Conceptual translation of the 4.2-kb cDNA revealed a single large open reading frame from a putative initiation codon. . . nucleotide 124 to an in-frame stop codon at nucleotide 3490. The inventors have determined the primary structure of the deduced \*\*receptor\*\* tyrosine kinase protein. The 1,122 residue polypeptide corresponds to a \*\*receptor\*\* tyrosine kinase protein containing a kinase region interrupted by a 21 amino acid insert linked via a transmembrane domain to . . .

SUMMARY:

BSUM(12)

The . . . the 4.2-kb cDNA encodes a 140-kDa protein that comigrates with a polypeptide specifically detected by antibody directed against the novel \*\*receptor\*\* tyrosine kinase protein in both cultured endothelial cells and highly vascularized embryonic tissues. A 140-kDa protein was also specifically precipitated. . .

SUMMARY:

BSUM(13)

The present inventors have further elucidated the role of the novel \*\*receptor\*\* tyrosine kinase within the endothelial cell lineage by disrupting its signalling pathway using two different genetic approaches. First, transgenic mice expressing a dominant-negative form of the novel \*\*receptor\*\* tyrosine kinase protein were constructed. Second, a null allele of the tek locus was created by homologous recombination in embryonic. . .

SUMMARY:

BSUM(14)

The . . . therefore provides a purified and isolated nucleic acid molecule, preferably a DNA molecule, having a sequence which codes for a \*\*receptor\*\* tyrosine kinase protein which is expressed in cells of endothelial lineage, or an oligonucleotide fragment of the nucleic acid molecules which is unique to the \*\*receptor\*\* tyrosine kinase protein of the invention. In a preferred embodiment of the invention, the purified and isolated nucleic acid molecule . . .

SUMMARY:

BSUM(16)

The . . . will hybridize to (a) or (b) under stringent conditions. In a particular embodiment, the fragment is a sequence encoding a \*\*receptor\*\* tyrosine kinase extracellular domain having the amino acid sequence as shown in SEQ ID NO:6 from amino acid number 19. . .

SUMMARY:

BSUM(21)

The invention further provides a method of preparing a novel \*\*receptor\*\* tyrosine kinase protein or isoforms thereof utilizing the purified and isolated nucleic acid molecule of the invention. The method comprises . . .

SUMMARY:

BSUM(22)

The invention further broadly contemplates a substantially pure \*\*receptor\*\* tyrosine kinase protein or a part thereof, which is expressed in cells of endothelial lineage.

SUMMARY:

BSUM(23)

The \*\*receptor\*\* tyrosine kinase protein of the invention is further characterized as containing an extracellular domain comprising at least one fibronectin III. . .

SUMMARY:

BSUM(24)

In . . . the protein having at least 20 amino acids. The part of the protein preferably comprises an extracellular domain of a \*\*receptor\*\* tyrosine kinase having the amino acid sequence as shown in SEQ ID NO:6 from amino acid number 19 to 744. . .

SUMMARY:

BSUM(25)

The present invention also includes a \*\*receptor\*\* tyrosine kinase protein of the invention or part thereof, preferably the catalytic domain, which is enzymatically active. The catalytically active form of the protein or part thereof is also referred to herein as an "activated \*\*receptor\*\* tyrosine kinase protein or part thereof".

SUMMARY:

BSUM(26)

The invention further contemplates antibodies having specificity against an epitope of the \*\*receptor\*\* tyrosine kinase protein of the invention or part of the protein. Antibodies may be labelled with a detectable substance and they may be used to detect the novel

\*\*receptor\*\* tyrosine kinase of the invention in tissues and cells. The antibodies may therefore be used to monitor angiogenesis, cardiogenesis and . . .

SUMMARY:

BSUM(27)

The invention also permits the construction of nucleotide probes which are unique to the novel \*\*receptor\*\* tyrosine kinase protein of the invention or a part of the protein. Thus, the invention also relates to a probe comprising a nucleotide sequence coding for a protein, which displays the properties of the novel \*\*receptor\*\* tyrosine kinase of the invention or a peptide unique to the protein. The probe may be labelled, for example, with . . . from a mixture of nucleotide sequences a nucleotide sequence coding for a protein which displays the properties of the novel \*\*receptor\*\* tyrosine kinase protein of the invention.

SUMMARY:

BSUM(28)

The . . . of the invention preferably a recombinant molecule comprising the nucleic acid molecules of the invention containing a sequence encoding the \*\*receptor\*\* tyrosine kinase protein of the invention or part thereof with a structural mutation or comprising the nucleic acid molecules of the invention containing a sequence encoding the \*\*receptor\*\* tyrosine kinase protein of the invention or part thereof and one or more regulatory elements which differ from the regulatory . . .

SUMMARY:

BSUM(29)

The invention still further provides a method for identifying a substance, which is capable of binding to the novel \*\*receptor\*\* tyrosine kinase protein of the invention, comprising reacting the novel \*\*receptor\*\* tyrosine kinase protein of the invention or part of the protein under conditions which permit the formation of a complex between the substance and the novel \*\*receptor\*\* tyrosine kinase protein or part of the protein and assaying for substance-\*\*receptor\*\* complexes, for free substance, for non-complexed \*\*receptor\*\* tyrosine kinase protein, or for activation of the \*\*receptor\*\* tyrosine kinase protein.

SUMMARY:

BSUM(30)

An embodiment of the invention provides a method for identifying ligands which are capable of binding to the novel \*\*receptor\*\* tyrosine kinase protein of the invention, isoforms thereof, or part of the protein, comprising reacting the novel \*\*receptor\*\* kinase protein of the invention, isoforms thereof, or part of the protein, with at least one ligand which potentially is capable of binding to the protein, isoform or part of the protein, under conditions which permit the formation of ligand-\*\*receptor\*\* protein complexes, and assaying for ligand-\*\*receptor\*\* protein complexes, for free ligand, for non-complexed proteins or for activation of the \*\*receptor\*\* tyrosine kinase protein. In a preferred embodiment of the method, ligands are identified which are capable of binding to and activating the novel \*\*receptor\*\* tyrosine kinase protein of the invention, isoforms thereof, or part of the protein. The ligands which bind to and activate the novel \*\*receptor\*\*

tyrosine kinase \*\*receptor\*\* of the invention are identified by assaying for protein tyrosine kinase activity i.e. by assaying for phosphotyrosine.

SUMMARY:

BSUM(31)

In . . . tek effector system. In accordance with one embodiment, a method is provided which comprises providing a known concentration of a \*\*receptor\*\* tyrosine kinase protein of the invention, or a part thereof, incubating the protein, or a part thereof, with a substance . . . thereby activating the tek effector system, and a suspected agonist or antagonist substance under conditions which permit the formation of ligand-\*\*receptor\*\* protein complexes, and assaying for ligand-\*\*receptor\*\* protein complexes, for free ligand or for non-complexed protein or for activation of the \*\*receptor\*\* tyrosine kinase protein.

SUMMARY:

BSUM(32)

The . . . a method for assaying a medium for the presence of an agonist or antagonist of the interaction of the novel \*\*receptor\*\* tyrosine kinase protein and a substance which is capable of binding to the \*\*receptor\*\* tyrosine kinase protein, which comprises providing a known concentration of the \*\*receptor\*\* tyrosine kinase protein, reacting the \*\*receptor\*\* tyrosine kinase protein with a substance which is capable of binding to the \*\*receptor\*\* tyrosine kinase protein and a suspected agonist or antagonist under conditions which permit the formation of substance-\*\*receptor\*\* tyrosine kinase complexes, and assaying for substance-\*\*receptor\*\* tyrosine kinase complexes, for free substance, for non-complexed proteins, or for activation of the \*\*receptor\*\* tyrosine kinase.

SUMMARY:

BSUM(33)

The . . . invention make it possible to screen a large number of potential ligands for their ability to bind to the novel \*\*receptor\*\* tyrosine kinase protein of the present invention. The methods of the invention will also be useful for identifying substances which . . .

SUMMARY:

BSUM(34)

Substances . . . may be identified using the methods of the invention by comparing the pattern and level of expression of the novel \*\*receptor\*\* tyrosine kinase protein of the invention in tissues and cells in the presence and in the absence of the substance.

SUMMARY:

BSUM(35)

The invention further contemplates a method for identifying a substance which is capable of binding to an activated \*\*receptor\*\* tyrosine kinase protein of the invention or an isoform or part of the activated protein, comprising reacting an activated \*\*receptor\*\* tyrosine kinase protein of the invention, or an isoform, or part of the protein, with at least one substance which potentially can bind with the \*\*receptor\*\* tyrosine kinase protein, isoform part of the protein, under conditions which permit the formation of substance-\*\*receptor\*\* kinase protein complexes,

and assaying for substance-\*\*receptor\*\* kinase protein complexes, for free substance, for non-complexed \*\*receptor\*\* kinase protein, or for phosphorylation of the substance. The method may be used to identify intracellular ligands such as Src homology region 2 (SH2) containing proteins which bind to an activated \*\*receptor\*\* tyrosine kinase of the invention or parts thereof or intracellular ligands which may be phosphorylated by the protein.

DRAWING DESC:

DRWD(3)

FIG. 1 shows a nucleotide and deduced amino acid sequence of a \*\*receptor\*\* tyrosine kinase protein of the invention as shown in SEQ ID NOS:1 and 2;

DRAWING DESC:

DRWD(5)

FIG. 3 shows a comparison of a portion of the deduced amino acid sequence of the novel \*\*receptor\*\* tyrosine kinase protein of the invention (SEQ ID NO:14) with that of other tyrosine kinases (SEQ ID NOS:15-17);

DRAWING DESC:

DRWD(35)

FIG. 12A shows a sequence comparison of Tek \*\*receptor\*\* tyrosine kinase protein (SEQ ID NOS:18-20 and Tie EGF-like repeats (SEQ ID NO:21-23;

DRAWING DESC:

DRWD(36)

FIG. 12B shows a sequence comparison of Tek \*\*receptor\*\* tyrosine kinase protein (SEQ. ID NOS: 26, 28 30) and Tie fibronectin type III repeats (SEQ ID NOS:27,29 and 31;

DRAWING DESC:

DRWD(75)

The present inventors have isolated a gene encoding a novel \*\*receptor\*\* tyrosine kinase protein, designated tek, expressed during murine cardiogenesis. By analysing the segregation of an AccI restriction site polymorphism in . . .

DRAWING DESC:

DRWD(77)

The novel gene products of the invention were identified as mouse \*\*receptor\*\* tyrosine kinase protein based on the structural homology of the protein to the known mouse and human \*\*receptor\*\* tyrosine kinases.

The deduced amino acid sequence of Tek protein predicts that it encodes a putative \*\*receptor\*\* tyrosine kinase that contains a 21 amino acid kinase insert and which is most closely related in its catalytic domain.

DRAWING DESC:

DRWD(79)

Overlapping . . . ID NO:5). The sequence of this cDNA predicts a 1122-residue protein having several structural motifs that distinguish it from other \*\*receptor\*\* tyrosine kinases. In particular the Tek tyrosine kinase protein has an extracellular domain within which three distinct types of structural . . . such as Drosophila leukocyte common

antigen-related molecule (DLAR) (SEQ ID NO:33) and fibronectin (FIG. 12B). The extracellular domain of Tek \*\*receptor\*\* tyrosine kinase represents a composite of three different structural motifs that are usually not found collectively within a single \*\*receptor\*\* tyrosine kinase.

DRAWING DESC:

DRWD(80)

It is likely that the unusual structure of the Tek \*\*receptor\*\* tyrosine kinase protein reflects some aspect of its role in endothelial cell biology. In addition to playing potential roles in regulating endothelial cell proliferation and differentiation, the complex structure of the Tek \*\*receptor\*\* tyrosine kinase protein extracellular domain likely also plays a role in guiding the proper patterning of endothelial cells during blood . . .

DRAWING DESC:

DRWD(81)

Tie, a \*\*receptor\*\* tyrosine kinase protein expressed in cells of the endothelial lineage (Partanen et al, 1992, Mol. Cell. Biol. 12:1698-1707) shows a similar juxtaposition of structural motifs within the extracellular domain as Tek \*\*receptor\*\* tyrosine kinase protein. Despite the structural homology between Tek and Tie proteins, these two molecules show only modest sequence similarity. . . within their carboxy terminal tails and kinase insert regions than in their ATP-binding and phosphotransferase domains, suggesting that these two \*\*receptors\*\* likely utilize non-identical signalling pathways.

DRAWING DESC:

DRWD(82)

A . . . carboxy terminal segment to which the antibody was raised (FIG. 15A, lane 3). The apparent size of the encoded Tek \*\*receptor\*\* tyrosine kinase protein, 140 kDa, is approximately 20 kDa greater than that predicted by the deduced amino acid sequence (126 kDa). The larger size of the detected protein indicates that Tek \*\*receptor\*\* tyrosine kinase protein may be a glycosylated cell surface protein.

DRAWING DESC:

DRWD(83)

Cell . . . Taken together, the results indicate that the 4.2 Kb tek cDNA contains the complete coding information for the native Tek \*\*receptor\*\* tyrosine kinase protein.

DRAWING DESC:

DRWD(84)

The . . . Tek antibody in both cultured endothelial cells (Py 4-1) and highly vascularized embryonic tissues (heart and umbilical vein). The Tek \*\*receptor\*\* tyrosine kinase protein cytoplasmic domain expressed in E. coli was shown to react with phosphotyrosine \*\*receptor\*\* tyrosine kinase protein antibodies.

DRAWING DESC:

DRWD(87)

Sequences . . . in SEQ ID NOS:1 and 5 or fragments thereof. An example of such a sequence includes the sequence encoding Tek \*\*receptor\*\* tyrosine kinase protein in humans and in other

meals.

DRAWING DESC:

DRWD(89)

The . . . 4 or 6. Substantially homologous sequences include sequences having at least 95% sequence homology. Peptides which are unique to the \*\*receptor\*\* tyrosine kinase protein of the invention are also contemplated, preferably peptides having at least 10 amino acids.

DRAWING DESC:

DRWD(92)

A . . . in FIGS. 1, 2 and 11B and these provide access to nucleotide sequences which code for polypeptides unique to the \*\*receptor\*\* tyrosine kinase protein of the invention. DNA sequences unique to the \*\*receptor\*\* tyrosine kinase protein of the invention or isoforms thereof, can also be constructed by chemical synthesis and enzymatic ligation reactions. . .

DRAWING DESC:

DRWD(93)

The present invention includes conjugates of the \*\*receptor\*\* tyrosine kinase protein of the invention. For example, the \*\*receptor\*\* tyrosine kinase protein or parts thereof may be conjugated with selected proteins to produce fusion proteins. Examples of proteins which. . .

DRAWING DESC:

DRWD(94)

ii. Expression Pattern of the \*\*Receptor\*\* Tyrosine Kinase protein of the invention

DRAWING DESC:

DRWD(95)

In . . . having an epithelial-like morphology and the requirement to contain fluid within an enclosed cavity. Thus, this tissue may utilize Tek \*\*receptor\*\* tyrosine kinase protein to accomplish this.

DRAWING DESC:

DRWD(96)

Specifically, . . . von Willebrand factor and appears to mark the embryonic progenitors of mature endothelial cells. Thus, tek encodes a novel putative \*\*receptor\*\* tyrosine kinase that may be critically involved in the determination and/or maintenance of cells of the endothelial lineage.

DRAWING DESC:

DRWD(99)

Several cell lines of endothelial origin were also examined for expression of tek and of Flk-1. Flk-1 encodes a \*\*receptor\*\* tyrosine kinase protein which is expressed in cells of the endothelial lineage.

Tek and Flk-1 were differentially expressed in endothelial. . .

DRAWING DESC:

DRWD(101)

The restricted expression of tek, imposes constraints on the cellular range of activity of the putative Tek \*\*receptor\*\* tyrosine kinase protein ligand, and suggests that the tek locus probably plays unique and important roles in the determination, migration, . . .

DRAWING DESC:

DRWD(104)

As hereinbefore mentioned, the present inventors have identified and sequenced a cDNA sequence encoding a novel \*\*receptor\*\* tyrosine kinase protein designated Tek.

DRAWING DESC:

DRWD(105)

Nucleic acid molecules of the present invention encoding the novel \*\*receptor\*\* tyrosine kinase protein of the present invention, or related, or analogous sequences, may be isolated and sequenced, for example, by . . . sequences of the clones obtained following amplification. Nucleic acid molecules of the present invention, or fragments thereof, encoding the novel \*\*receptor\*\* tyrosine kinase protein of the present invention, or parts thereof, may also be constructed by chemical synthesis and enzymatic ligation. . .

DRAWING DESC:

DRWD(106)

The nucleic acid molecules of the present invention having a sequence which codes for the \*\*receptor\*\* tyrosine kinase protein of the invention, or an oligonucleotide fragment of the nucleic acid molecules may be incorporated in a . . .

DRAWING DESC:

DRWD(107)

The Tek \*\*receptor\*\* tyrosine kinase protein or isoforms or parts thereof, may be obtained by expression in a suitable host cell using techniques. . .

DRAWING DESC:

DRWD(108)

DNA sequences encoding Tek \*\*receptor\*\* tyrosine kinase protein, or a part thereof, may be expressed by a wide variety of prokaryotic and eukaryotic host cells. . .

DRAWING DESC:

DRWD(114)

Tek \*\*receptor\*\* tyrosine kinase protein may be prepared by culturing the host/vector systems described above, in order to express the recombinant Tek \*\*receptor\*\* tyrosine kinase protein.

DRAWING DESC:

DRWD(115)

Conjugates of Tek \*\*receptor\*\* tyrosine kinase protein of the invention, or parts thereof, with other molecules, such as proteins or polypeptides, may be prepared. . . C-terminal fusion proteins. Thus, fusion proteins may be prepared by fusing, through recombinant techniques, the N-terminal or C-terminal of Tek \*\*receptor\*\* tyrosine kinase protein or parts thereof, and the sequence of a selected protein with a desired biological function. The resultant fusion proteins contain Tek \*\*receptor\*\* tyrosine kinase protein or a portion thereof fused to the selected protein. Examples of proteins which may be selected to. . .

DRAWING DESC:

DRWD(117)

Within . . . cloned tek cDNA as a template. In particular, the Tek fusion protein is synthesized from the extracellular domain of Tek \*\*receptor\*\* tyrosine kinase protein (amino acids 19 to 744,

SEQ ID NO:6  
and FIG. 11B).

DRAWING DESC:

DRWD(120)

Phosphorylated \*\*receptor\*\* tyrosine kinase proteins of the invention, or parts thereof, may be prepared using the method described in Reedijk et al. . . tyrosine kinase. Bacteria containing the plasmid and bacteriophage as a lysogen are isolated. Following induction of the lysogen, the expressed \*\*receptor\*\* protein becomes phosphorylated.

DRAWING DESC:

DRWD(123)

The . . . may be used to detect genes, preferably in human cells, that encode proteins related to, or analogous to, the novel \*\*receptor\*\* tyrosine kinase protein of the invention.

DRAWING DESC:

DRWD(124)

The \*\*receptor\*\* tyrosine kinase protein of the invention or parts thereof, for example amino acids of the extracellular domain, carboxy terminal tail or catalytic domain, may be used to prepare monoclonal or polyclonal antibodies. Antibodies having specificity for Tek \*\*receptor\*\* tyrosine kinase protein may also be raised from fusion proteins created by expressing trpE-Tek fusion proteins in bacteria as described. . .

DRAWING DESC:

DRWD(125)

Within . . . antibodies, antibody fragments (e.g., Fab, and F(ab)<sub>2</sub>) and recombinantly produced binding partners. Antibodies are understood to be reactive against Tek \*\*receptor\*\* tyrosine kinase protein if they bind with a K<sub>sub</sub>a of greater than or equal to 10<sup>-7</sup> M. As will be. . .

DRAWING DESC:

DRWD(130)

The polyclonal or monoclonal antibodies may be used to detect the \*\*receptor\*\* tyrosine kinase protein of the invention in various biological materials, for example they may be used in an Elisa, radioimmunoassay or histochemical tests. Thus, the antibodies may be used to quantify the amount of a \*\*receptor\*\* tyrosine kinase protein of the invention in a sample in order to determine its role in particular cellular events or. . .

DRAWING DESC:

DRWD(131)

In . . . the invention may be used in immuno-histochemical analyses, for example, at the cellular and sub-subcellular level, to detect the novel \*\*receptor\*\* tyrosine kinase protein of the invention, to localise it to particular cells and tissues and to specific subcellular locations, and to. . .

DRAWING DESC:

DRWD(132)

Cytological . . . kinase of the invention. Generally, an antibody of the invention may be labelled with a detectable substance and the novel \*\*receptor\*\* tyrosine kinase of the invention may be localised in tissue

based upon the presence of the detectable substance. Examples of . . .

DRAWING DESC:

DRWD(139)

The finding of a novel \*\*receptor\*\* tyrosine kinase which is only expressed in cells of the endothelial lineage permits the identification of substances such as ligands, . . . and natural and synthetic derivatives of such ligands, which are capable of binding to, and in some cases activating the \*\*receptor\*\* tyrosine kinase protein of the invention, isoforms thereof, or part of the protein may be identified. The method involves reacting the novel \*\*receptor\*\* kinase protein of the invention, isoforms thereof, or part of the protein with at least one ligand which potentially is capable of binding to the protein, isoform or part of the protein, under conditions which permit the formation of ligand-\*\*receptor\*\* protein complexes, and assaying for ligand-\*\*receptor\*\* protein complexes, for free ligand or for non-complexed proteins or for activation of the \*\*receptor\*\* tyrosine kinase.

DRAWING DESC:

DRWD(140)

The ligand-\*\*receptor\*\* protein complexes, free ligand or non-complexed proteins \*\*receptor\*\*-ligand complex, may be isolated by conventional isolation techniques, for example, salting out, chromatography, electrophoresis, gel filtration, fractionation, absorption, polyacrylamide gel electrophoresis, agglutination, or combinations thereof. To facilitate the assay of the components, antibody against the \*\*receptor\*\* protein or the ligand, or a labelled \*\*receptor\*\* protein, or a labelled ligand may be utilized. Antibodies, \*\*receptor\*\* protein, or substance may be labelled with a detectable substance as described above.

DRAWING DESC:

DRWD(141)

The \*\*receptor\*\* tyrosine kinase protein, isoforms or parts thereof, or ligand used in the method of the invention may be insolubilized. For example, the \*\*receptor\*\* protein or ligand may be bound to a suitable carrier. Examples of suitable carriers are agarose, cellulose, dextran, Sephadex, Sepharose, . . . etc. The carrier may be in the shape of, for example, a tube, test plate, beads, disc, sphere etc. Insolubilized \*\*receptor\*\* tyrosine kinase protein or ligand thereof will include \*\*receptor\*\* tyrosine kinase protein or ligand thereof expressed on the surface of a cell.

DRAWING DESC:

DRWD(142)

The insolubilized \*\*receptor\*\* tyrosine kinase protein or ligand may be prepared by reacting the material with a suitable insoluble carrier using known chemical. . .

DRAWING DESC:

DRWD(143)

Conditions which permit the formation of ligand-\*\*receptor\*\* protein complexes may be selected having regard to factors such as the nature and amounts of the ligand and the \*\*receptor\*\* protein.

DRAWING DESC:

DRWD(144)

The \*\*receptor\*\* tyrosine kinase protein, parts thereof, or substances may also be expressed on the surface of a cell using the methods. . .

DRAWING DESC:

DRWD(145)

In a preferred embodiment of the method, ligands are identified which are capable of binding to and activating the novel \*\*receptor\*\* tyrosine kinase protein of the invention. In this method the ligands which bind to and activate the novel \*\*receptor\*\* tyrosine kinase protein of the invention are identified by assaying for protein tyrosine kinase activity i.e. by assaying for phosphorylation of the tyrosine residues of the \*\*receptor\*\*.

DRAWING DESC:

DRWD(147)

The ligands for many \*\*receptor\*\* tyrosine kinase proteins are cell-bound, either as they are associated with the cell surface via heparin and hepatocyte growth factor. . . Accordingly, a ligand for Tek protein may have a cell-bound form. A cell-bound ligand may be identified by reacting the \*\*receptor\*\* tyrosine kinase protein of the invention, an isoform or a part thereof with a cell suspected of expressing the ligand. . .

DRAWING DESC:

DRWD(151)

The term "tek effector system" used herein refers to the interactions of a ligand, and the \*\*receptor\*\* tyrosine kinase protein of the invention, and includes the binding of a ligand to the \*\*receptor\*\* protein or any modifications to the \*\*receptor\*\* associated therewith, to form a ligand-\*\*receptor\*\* complex and activating tyrosine kinase activity thereby affecting signalling pathways, particularly those involved in the regulation of angiogenesis.

DRAWING DESC:

DRWD(152)

In accordance with one embodiment, a method is provided which comprises providing a known concentration of a \*\*receptor\*\* tyrosine kinase protein of the invention, isoforms thereof, or part of the protein, incubating the protein, isoforms thereof, or part . . . thereof, or part of the protein, and a suspected agonist or antagonist substance under conditions which permit the formation of ligand-\*\*receptor\*\* protein complexes, and assaying for ligand-\*\*receptor\*\* protein complexes, for free ligand or for non-complexed proteins.

DRAWING DESC:

DRWD(153)

The ligand-\*\*receptor\*\* complex, free ligand or non-complexed proteins may be assayed as described above. Suitable ligands used in the assay method may . . .

DRAWING DESC:

DRWD(154)

The . . . the invention may be used to assay for a substance that competes for the same ligand-binding site on the novel \*\*receptor\*\*.

tyrosine kinase protein of the invention.

DRAWING DESC:

DRWD(155)

It . . . be assayed using the methods of the invention may act on one or more of the binding sites on the \*\*receptor\*\* tyrosine kinase or the ligand, including agonist binding sites, competitive antagonist binding sites, non-competitive antagonist binding sites or allosteric sites.

DRAWING DESC:

DRWD(156)

The . . . invention make it possible to screen a large number of potential ligands for their ability to bind to the novel \*\*receptor\*\* tyrosine kinase protein of the present invention. The methods of the invention are therefore useful for identifying potential stimulators or . . .

DRAWING DESC:

DRWD(157)

The invention further contemplates a method for identifying a substance which is capable of binding to an activated \*\*receptor\*\* tyrosine kinase protein of the invention or an isoform or part of the activated protein, comprising reacting an activated \*\*receptor\*\* tyrosine kinase protein of the invention, or an isoform, or part of the protein, with at least one substance which potentially can bind with the \*\*receptor\*\* tyrosine kinase protein, isoform or part of the protein, under conditions which permit the formation of substance-\*\*receptor\*\* kinase protein complexes, and assaying for substance-\*\*receptor\*\* kinase protein complexes, for free substance, for non-complexed \*\*receptor\*\* kinase proteins, or for phosphorylation of the substance.

DRAWING DESC:

DRWD(158)

An activated \*\*receptor\*\* tyrosine kinase protein of the invention, or isoform or part thereof may be prepared by binding of a ligand to the extracellular domain of a \*\*receptor\*\* tyrosine kinase protein of the invention which results in activation of the catalytic domain. Such a ligand may be identified using the methods hereinbefore described. An activated \*\*receptor\*\* or part thereof, may also be prepared using the methods described for example in Reedijk et al. The EMBO Journal, 11(4):1365, 1992 for producing a tyrosine phosphorylated \*\*receptor\*\* or part thereof.

DRAWING DESC:

DRWD(159)

Conditions which permit the formation of substance-\*\*receptor\*\* protein complexes may be selected having regard to factors such as the nature and amounts of the substance and the \*\*receptor\*\* protein. The substance-\*\*receptor\*\* complex, free substance or non-complexed proteins may be isolated by conventional isolation techniques described above. Phosphorylation of the substance may . . .

DRAWING DESC:

DRWD(160)

In . . . this method, intracellular ligands such as Src

homology  
region 2 (SH2)-containing proteins which are capable of binding to a phosphorylated \*\*receptor\*\* tyrosine kinase protein of the invention may be identified. SH2-containing proteins refers to proteins containing a Src homology region 2 . . . the role of SH2 domains). SH2-containing proteins may function downstream of the Tek signalling pathway by binding to the activated \*\*receptor\*\* protein. Intracellular ligands which may be phosphorylated by the novel \*\*receptor\*\* tyrosine kinase protein of the invention may also be identified using the method of the invention.

DRAWING DESC:

DRWD(161)

The . . . tissue of an animal, a substance suspected of affecting angiogenesis, cardiogenesis, or tumorigenesis and detecting, and optionally quantitating, the novel \*\*receptor\*\* tyrosine kinase of the invention in the non-human animal or tissue.

DRAWING DESC:

DRWD(166)

By way of example, specific targeted mutations maybe employed to generate a Tek \*\*receptor\*\* tyrosine kinase protein that is still competent to bind ligand, but which is unable to transduce a signal due to . . .

DETDESC:

DETD(26)

To . . . RT-PCR). Four of these cDNAs represented previously characterized tyrosine kinases including, bmk, c-src, c-abl, and the platelet derived growth factor \*\*receptor\*\* .beta.-subunit (pdgfb). The isolation of bmk, c-src, and c-abl is consistent with the broad tissue distribution of these kinases (Wang, . . .

DETDESC:

DETD(30)

Comparison . . . (FIG. 3) reveals that the deduced tek amino acid sequence shows 42% sequence identity to the mouse fibroblast growth factor \*\*receptor\*\* Flg (Reid et al., 1990; Safran, A., Avivi, A., On-Utereger, A., Neufeld, G., Lonai, P., Givoli, D. & Yarden, Y. . . Maniatis, T. (1989). Molecular Cloning. Cold Spring Harbor Laboratory Press) and 45% to the transmembrane RTK encoded by the human \*\*c-e\*\*-\*\*ret\*\* protooncogene (Takahashi & Cooper, 1987). In addition, striking sequence identity is observed to a 65 amino acid residue sequence encoded. . .

DETDESC:

DETD(91)

The extracellular domain of Tek \*\*receptor\*\* tyrosine kinase protein is, therefore, particularly complex, representing a composite of three different structural motifs that are usually not found. . .

DETDESC:

DETD(92)

Anchoring of Tek \*\*receptor\*\* tyrosine kinase protein in the membrane is most probably achieved by the highly hydrophobic stretch of residues that extends between . . .

DETDESC:

DETD(93)

The catalytic region of Tek \*\*receptor\*\* tyrosine kinase protein, which starts at residue 829, is interrupted by a 21-amino acid insert at residue 913 (SEQ ID . . . et al., 1992). However, Tek does contain a 32-amino acid residue carboxyl tail that contains tyrosine residues (FIG. 11B). Tek \*\*receptor\*\* tyrosine kinase protein may therefore mediate signal transduction by binding of downstream signalling molecules to these tyrosine residues when they. . .

DETDESC:

DETD(99)

Expression of Tek \*\*receptor\*\* tyrosine kinase protein

DETDESC:

DETD(100)

To . . . a mammalian expression vector containing tek (as described above). Cell extracts prepared from metabolically labelled transfecants were analyzed for Tek \*\*receptor\*\* tyrosine kinase protein expression by immunoprecipitation with affinity-purified antibody directed against the carboxy terminal 43-amino acid residues.

DETDESC:

DETD(101)

FIGS. . . Py4-1 cells, and Day 13.5 embryonic heart tissue (lanes 1 to 5, respectively) were analyzed for the presence of Tek \*\*receptor\*\* tyrosine kinase protein using affinity purified Tek antibodies.

DETDESC:

DETD(103)

The . . . slightly faster migrating species was also detected in Py4-1 cells. This species most likely represents an incompletely glycosylated form of Tek \*\*receptor\*\* tyrosine kinase protein, although it may be a distinct cross-reacting polypeptide. Taken together, these results indicate that the tek cDNA shown in SEQ ID NO: 5 and FIG. 11B contains the complete coding information for the native Tek \*\*receptor\*\* tyrosine kinase protein.

DETDESC:

DETD(106)

Tek . . . unlike all previously described members of the RTK family, encoded a molecule with virtually the same multidomain structure as Tek \*\*receptor\*\* tyrosine kinase protein. In fact, comparison of the primary structure of Tek and Tie proteins revealed considerable sequence similarity in . . .

DETDESC:

DETD(107)

FIGS. . . described in respect to FIG. 11A and the numbers denote per cent sequence similarity between corresponding regions of the two \*\*receptors\*\*. The bar indicates the cDNA region of tek and tie used as probes in panel B. FIG. 13B shows a . . .

DETDESC:

DETD(113)

The . . . et al., 1992; Taguchi et al., 1993; Olopade et al., 1992; Rowley and Diaz, 1992). The latent oncogenic potential of \*\*receptor\*\* tyrosine kinase proteins and their known activation or gene amplification

in malignancy suggests that if Tek \*\*receptor\*\* tyrosine kinase protein is indeed playing a role in these neoplasms it is most likely not due to a loss. . .

DETDESC:

DETD(121)

Generation of Transgenic Mice Carrying a tek cDNA Encoding a Dominant-Negative Tek \*\*Receptor\*\* Tyrosine Kinase Protein

DETDESC:

DETD(128)

Based on the assumption that Tek \*\*receptor\*\* tyrosine kinase may play a critical role in the endothelial cell lineage, transgenic founder embryos were removed on Days 9.5. . .

CLAIMS:

CLMS(1)

We claim:

1. A purified and isolated nucleic acid molecule comprising a sequence encoding Tek \*\*receptor\*\* tyrosine kinase protein having the amino acid sequence as shown in SEQ ID NO: 2.

CLAIMS:

CLMS(2)

2. . . and isolated nucleic acid molecule comprising the nucleic acid sequence as shown in SEQ ID NO:1 which encodes a Tek \*\*receptor\*\* tyrosine kinase protein.

CLAIMS:

CLMS(5)

5. A method for preparing a Tek \*\*receptor\*\* tyrosine kinase protein comprising inserting a nucleic acid molecule as claimed in claim 1 or 2 into an expression vector, . . . transfected the expression vector into a host cell, culturing the host cell under conditions allowing for expression of the Tek \*\*receptor\*\* tyrosine kinase protein, and recovering the Tek \*\*receptor\*\* tyrosine kinase protein.

CLAIMS:

CLMS(6)

6. A purified and isolated nucleic acid molecule comprising a sequence encoding a fragment of Tek \*\*receptor\*\* tyrosine kinase protein said fragment consisting of the amino acid sequence as shown in SEQ ID NO:4.

CLAIMS:

CLMS(7)

7. A purified and isolated nucleic acid molecule comprising a sequence encoding a fragment of Tek \*\*receptor\*\* tyrosine kinase protein said sequence consisting of the nucleic acid sequence as shown in SEQ ID NO:3.

CLAIMS:

CLMS(9)

9. . . sequence encoding amino acids 19 to 744 as shown in SEQ ID NO:2 which is the extracellular domain of Tek \*\*receptor\*\* tyrosine kinase protein.

CLAIMS:

CLMS(11)

11. A purified and isolated nucleic acid molecule comprising a sequence encoding an immunoglobulin-like loop in the extracellular domain of Tek \*\*receptor\*\* tyrosine kinase protein having the amino acid sequence of amino acids 19 to 209 as shown in SEQ ID NO:2.

CLAIMS:

CLMS(12)

12. A purified and isolated nucleic acid molecule comprising a sequence encoding an immunoglobulin-like loop in the extracellular domain of Tek \*\*receptor\*\* tyrosine kinase protein having the amino acid sequence of amino acids 344 to 467 as shown in SEQ ID NO:2.

CLAIMS:

CLMS(13)

13. A purified and isolated nucleic acid molecule comprising a sequence encoding Tek \*\*receptor\*\* tyrosine kinase protein having the amino acid sequence as shown in SEQ ID NO:6.

CLAIMS:

CLMS(14)

14. A purified and isolated nucleic acid molecule comprising which encodes a Tek \*\*receptor\*\* tyrosine kinase protein the nucleic acid sequence as shown in SEQ ID NO:5.

8. 5,658,791, Aug. 19, 1997, Antibodies which specifically bind to proteins having tyrosine kinase activity, wherein said proteins have more than one tyrosine kinase domain, and no SH2 domains; Andrew Frederick Wilks, et al., 435/331, 338; 530/387.9, 388.1, 388.25, 388.26, 388.85, 389.1 [IMAGE AVAILABLE]

US PAT NO: 5,658,791 [IMAGE AVAILABLE] L9: 8 of 10

SUMMARY:

BSUM(2)

Protein tyrosine kinases (PTKs) are structurally well suited to a role in intracellular signal transduction. Many growth factor \*\*receptors\*\*, for example, transduce the extracellular stimulus they receive through interaction with their cognate ligand via an intracellular tyrosine kinase domain. At least one of the non-\*\*receptor\*\* PTKs, namely LCK, is believed to mediate the transduction in T-cells of a signal from the interaction of a cell-surface. . .

SUMMARY:

BSUM(3)

The . . . this family can be employed in a variety of cellular contexts. Similar PTK structural sub-families exist based around the FGF \*\*receptor\*\* and the CSF-1 \*\*receptor\*\* (reviewed in Wilks, 1990).

DRAWING DESC:

DRWD(15)

FIG. . . of structural similarity, branch length a function of sequence identity. The abbreviations used are: SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R=Colony stimulating factor-1 receptor; KIT=c-kit; PDGF-R=Platelet derived growth factor receptor-A; RET=c-ret; ANP-A=Atrial natriuretic peptide receptor-A; ANP-B=Atrial natriuretic peptide receptor-B; MOS=c-mos; PBS2=polyxin B antibiotic resistance gene product; STE7=sterile mutant wild-type allele gene . . .

TABLE III

product; JAK1/1=Domain-1 of Human JAK1; JAK1/2=PTK domain or . . .

DETDESC:

DETD(30)

The . . . 1988) and the phospholipase-C family of proteins (Suh et al., 1988). This is a particularly interesting observation since no other non-\*\*receptor\*\* PTK has been described which lacks this feature. A hydrophilicity plot failed to demonstrate the presence of a hydrophobic domain characteristic of the growth factor \*\*receptor\*\* type of PTK (FIG. 3b) suggesting that this protein is wholly intracellular like other members of the non-\*\*receptor\*\* class of PTKs. The one outstanding feature of the JAK1 hydrophathy plot is the highly hydrophilic sequence between residues 320-350. . . .

DETDESC:

DETD(37)

The . . . which pre-dated the development of the PTK sub-family. It is of interest to note that the kinase-related domains of the ANP-\*\*receptor\*\*/guanylate cyclase family diverge at a point close by.

9. 5,514,546, May 7, 1996, Stem-loop oligonucleotides containing parallel and antiparallel binding domains; Eric T. Kool, 435/6, 536/23.1, 24.3 [IMAGE AVAILABLE]

US PAT NO: 5,514,546 [IMAGE AVAILABLE] L9: 9 of 10

DETDESC:

DETD(78)

Other ligands for cellular \*\*receptors\*\* may also have utility for improving cellular uptake, including, e.g. insulin, transferrin and others. Similarly, derivatization of oligonucleotides with poly-L-lysine. . . .

DETDESC:

DETD(112)

Moreover. . . c-ets, c-igf, c-fms, c-fos, c-has/bas, her-2 neu, c-int, c-jun, c-kit, c-mas, c-met, c-mos, c-myb, c-myc, N-myc, p53, ras, c-Ha-ras, c-rel, \*\*c\*\*-\*\*ret\*\*\*, c-ros, c-sec, c-sis, c-ski, c-snoA, c-snoN, c-spi, c-src, c-syn, c-trk, c-vav and c-yes.

10. 5,466,596, Nov. 14, 1995, Tissue specific transcriptional regulatory element; Martin L. Breitman, et al., 435/354, 69.1, 70.3; 536/24.1 [IMAGE AVAILABLE]

US PAT NO: 5,466,596 [IMAGE AVAILABLE] L9: 10 of 10

DRAWING DESC:

<-----User Break----->  
u

DETDESC:

=>  
=> d 1B cit kwic 1-24

1. 5,945,402, Aug. 31, 1999, Human relaxin formulation; David C Cipolla, et al., 514/21; 530/366, 399 [IMAGE AVAILABLE]

US PAT NO: 5,945,402 [IMAGE AVAILABLE] L8: 1 of 24

DETDESC:

DETD(70)

REVERSE PHASE HPLC  
STABILITY OF CITRATE FORMULATION STORED AT 5.degree. \*\*C\*\*.

\*\*Ret\*\*. Time  
Area (main Total Fraction  
Time (days)  
(min.) peak times. 10  
Area times. 10  
Main Peak. . .

DETDESC:

DETD(71)

TABLE IV

REVERSE PHASE HPLC  
STABILITY OF CITRATE FORMULATION STORED AT -20.degree. \*\*C\*\*.

\*\*Ret\*\*. Time Area (main Total Fraction  
Time (days)  
(min.) peak times. 10  
Area times. 10  
Main Peak. . .

DETDESC:

DETD(81)

TABLE V

REVERSE PHASE HPLC (FREEZE-THAW)  
STABILITY OF CITRATE FORMULATION STORED AT -20.degree. \*\*C\*\*.

\*\*Ret\*\*. Time Area (main Total Fraction  
Time (days)  
(min.) peak times. 10  
Area times. 10  
Main Peak

2. 5,910,426, Jun. 8, 1999, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 435/68.1; 530/402 [IMAGE AVAILABLE]

US PAT NO: 5,910,426 [IMAGE AVAILABLE] L8: 2 of 24

DRAWING DESC:

DRWD(15)

FIG. . . of sequence identity. The abbreviations used are: SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R=Colony stimulating factor-1 receptor; KIT=c-kit; PDGF-R=Platelet derived growth factor receptor-A; RET=c-ret; ANP-A=Atrial natriuretic peptide receptor-A; ANP-B=Atrial natriuretic peptide receptor-B; MOS=c-mos; PBS2=polyxin B antibiotic resistance gene product; STE7=sterile mutant wild-type allele gene. . .

3. 5,882,923, Mar. 16, 1999, Glial cell line-derived neurotrophic factor regulation of ureteric budding and growth; Hannu Sariola, et al., 435/325, 368, 369, 375, 384; 514/2 [IMAGE AVAILABLE]

US PAT NO: 5,882,923 [IMAGE AVAILABLE] L8: 3 of 24

DETDESC:

DETD(17)

Agarose . . . not observed in explants ret.k homozygous embryos, suggesting that the lack of response is exclusively due to the absence of \*\*c\*\*-\*\*ret\*\* receptor tyrosine kinase, and that normal \*\*c\*\*-\*\*ret\*\* functioning is necessary for GDNF signaling in the peripheral nervous system.

DETDESC:

DETD(40)

We . . . NO:2]. The identity of the cloned fragment was verified by

direct sequencing with a Pharmacia A.L.F. automatic DNA sequencer. The \*\*c\*\*-\*\*ret\*\* probe spanned the tyrosine kinase domain of mouse \*\*c\*\*-\*\*ret\*\* (nucleotides 2534-3217; Pachnis et al., 1993). The cloning of rat GDNF probe for *in situ* hybridisation has been described in . . .

#### DETDESC:

DETD(95)  
Liu, . . . A., Carone, F. A., Takahashi, M. and Kanwar Y. S. (1996). Comparative role of phosphotyrosine kinase domains of c-ros and \*\*c\*\*-\*\*ret\*\* protooncogenes in metanephric development with respect to growth factors and matrix morphogens. *Devel. Biol.* 178, 133-148.

4. 5,852,184, Dec. 22, 1998, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 536/23.4; 435/194, 320.1; 536/23.1 [IMAGE AVAILABLE]

US PAT NO: 5,852,184 [IMAGE AVAILABLE] L8:  
4 of 24

#### SUMMARY:

BSUM(42)

FIG. . . . of sequence identity. The abbreviations used are: SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R=Colony stimulating factor-1 receptor; KIT=c-kit; PDGF-R=Platelet derived growth factor receptor-A; RET=\*\*c\*\*-\*\*RET\*\*; ANP-A=Atrial natriuretic peptide receptor-A; ANP-B=Atrial natriuretic peptide receptor-B; MOS=c-mos; PBS2=polyxyn B antibiotic resistance gene product; STE7=sterile mutant wild-type allele gene. . .

5. 5,821,069, Oct. 13, 1998, Method for determining tyrosine kinase in a sample; Andrew Frederick Wilks, et al., 435/7.21; 530/387.9, 388.1, 388.25, 388.26, 388.85, 389.1 [IMAGE AVAILABLE]

US PAT NO: 5,821,069 [IMAGE AVAILABLE] L8:  
5 of 24

#### DRAWING DESC:

DRWD(15)

FIG. . . . SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R=Colony stimulating factor-1 receptor; KIT=c-kit; PDGF-R=Platelet derived growth factor receptor-A; RET=\*\*c\*\*-\*\*RET\*\*; ANP-A=Atrial natriuretic peptide receptor-A; ANP-B=Atrial natriuretic peptide receptor-B; MOS=c-mos; PBS2=polyxyn B antibiotic resistance gene product; STE7=sterile mutant wild-type allele gene. . .

6. 5,808,036, Sep. 15, 1998, Stem-loop oligonucleotides containing parallel and antiparallel binding domains; Eric T. Kool, 536/24.3; 435/6, 320.1, 325, 375; 536/23.1, 24.5 [IMAGE AVAILABLE]

US PAT NO: 5,808,036 [IMAGE AVAILABLE] L8:  
6 of 24

#### DETDESC:

DETD(118)

Moreover, . . . c-ets, c-gf, c-fms, c-fos, c-has/bas, her-2 neu, c-int, c-jun, c-kit, c-mas, c-met, c-mos, c-myb, c-myc, N-myc, p53, ras, c-Ha-ras, c-rel, \*\*c\*\*-\*\*ret\*\*; c-ros, c-sec, c-sis, c-ski, c-snoA, c-snoN, c-spi, c-src, c-syn, c-trk, c-vav and c-yes.

7. 5,805,885, Sep. 8, 1998, Method and system for aggregating objects; Paul Leach, et al., 709/303 [IMAGE AVAILABLE]

US PAT NO: 5,805,885 [IMAGE AVAILABLE] L8:  
7 of 24

#### DETDESC:

DETD(21)  
. . .

friend B;  
B m.sub.-- B;  
public:

virtual boolean QueryInterface(REFIID iid, void \*\*ppv)\*\*  
\*\*{ ret = TRUE;\*\*  
\*\*switch (iid)\*\*  
\*\*{ case IID\_sub.-- \*\*C\*\*:\*\*  
\*\* "ret" = m.sub.-- punkS1->QueryInterface(iid,  
ppv);\*\*  
\*\* break;\*\*  
\*\*case IID\_sub.-- F:\*\*  
\*\* ret = m.sub.-- punkS2->QueryInterface(iid, ppv);\*\*  
\*\* break;\*\*  
\*\*case IID\_sub.-- A:\*\*  
\*\* . . . \*\*  
\*\* . . . \*\*

\*\*8. 5,745,764, Apr. 28, 1998, Method and system for aggregating objects;\*\*

\*\*Paul Leach, et al., 709/303 [IMAGE AVAILABLE]\*\*  
. . .

\*\*US PAT NO: 5,745,764 [IMAGE AVAILABLE]

L8: 8 of 24\*\*

\*\*. . . \*\*

\*\*DETDESC: \*\*

\*\*. . . \*\*

\*\*DETD(21)\*\*

\*\*. . . \*\*

\*\*B;  
\*\*B m.sub.-- B;\*\*

\*\*public: \*\*

\*\*virtual boolean QueryInterface(REFIID iid, void \*\*ppv)  
{ ret = TRUE;  
switch (iid)  
( case IID\_sub.-- \*\*C\*\*:.  
\*\* "ret" = m.sub.-- punkS1->QueryInterface(iid, ppv);  
break;  
case IID\_sub.-- F:  
ret = m.sub.-- punkS2->QueryInterface(iid, ppv);  
break;  
case IID\_sub.-- A: . . .

9. 5,716,818, Feb. 10, 1998, Protein tyrosine kinase; Andrew Frederick Wilks, et al., 435/194; 530/326, 328, 329, 350 [IMAGE AVAILABLE]

US PAT NO: 5,716,818 [IMAGE AVAILABLE] L8:  
9 of 24

#### DRAWING DESC:

DRWD(14)

FIG. . . . of sequence identity. The abbreviations used are: SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R=Colony stimulating factor-1 receptor; KIT=c-kit; PDGF-R=Platelet derived growth factor receptor-A; RET=\*\*c\*\*-\*\*RET\*\*; ANP-A=Atrial natriuretic peptide receptor-A; ANP-B=Atrial natriuretic peptide receptor-B; MOS=c-mos; PBS2=polyxyn B antibiotic resistance gene product; STE7=sterile mutant wild-type allele gene. . .

10. 5,710,925, Jan. 20, 1998, Method and system for aggregating objects;

Paul Leach, et al., 709/303; 707/103 [IMAGE AVAILABLE]

US PAT NO: 5,710,925 [IMAGE AVAILABLE] L8:  
10 of 24

#### DETDESC:

DETD(21)

. . .  
B m.sub.-- B;  
public:  
virtual boolean QueryInterface(REFIID iid, void \*\*ppv)\*\*  
\*\*{ ret = TRUE;\*\*  
\*\* switch (iid)\*\*  
\*\* { case IID\_sub.-- \*\*C\*\*:\*\*  
\*\* "ret" = m.sub.-- punkS1->QueryInterface(iid,  
ppv);\*\*  
\*\* break;\*\*  
\*\* case IID\_sub.-- F:\*\*  
\*\* ret = m.sub.-- punkS2->QueryInterface(iid, ppv);\*\*  
\*\* break;\*\*  
\*\* case IID\_sub.-- A: . . . \*\*  
\*\* . . . \*\*

\*\*11. 5,681,714, Oct. 28, 1997, Nucleic acid encoding tek receptor\*\*

\*\*tyrosine kinase; Martin L. Breitman, deceased, et al., 435/69.1, 194,\*\*

\*\*252.3, 254.11, 320.1, 325, 352, 358, 365, 367 [IMAGE AVAILABLE]\*\*  
. . .

\*\*. . .

\*\*US PAT NO: 5,681,714 [IMAGE AVAILABLE]

L8: 11 of 24\*\*

\*\*. . .

\*\*DETDESC: \*\*

\*\*. . .

\*\*DETD(30)\*\*

\*\*. . .

\*\* Comparison . . . Maniatis, T. (1989). Molecular Cloning. Cold Spring\*\*

\*\*Harbor Laboratory Press) and 45% to the transmembrane RTK encoded by the\*\*

\*\*"human \*\*c\*\*-\*\*ret\*\* protooncogene (Takahashi & Cooper, 1987), In\*\*

\*\*addition, striking sequence identity is observed to a 65 amino acid\*\*

\*\*residue sequence encoded. . . .\*\*

\*\*. . .

\*\*12. 5,658,791, Aug. 19, 1997, Antibodies which specifically bind to\*\*

\*\*proteins having tyrosine kinase activity, wherein said proteins have more\*\*

\*\*than one tyrosine kinase domain, and no SH2 domains; Andrew Frederick\*\*

\*\*Wilks, et al., 435/331, 338; 530/387.9, 388.1, 388.25, 388.26, 388.85,\*\*

\*\*389.1 [IMAGE AVAILABLE]\*\*

\*\*. . .

\*\*US PAT NO: 5,658,791 [IMAGE AVAILABLE]

L8: 12 of 24\*\*

\*\*. . .

\*\*DRAWING DESC: \*\*

\*\*. . .

\*\*DRWD(15)\*\*

\*\*. . .

\*\* FIG. . . . of sequence identity. The abbreviations used are:\*\*

\*\*SRC=c-src; YES=c-Yes; FES=c-fes; CSF1-R=Colony

stimulating factor-1\*\*

\*\*receptor; KIT=c-kit; PDGF-R=Platelet derived growth factor receptor-A;\*\*

\*\*RET=\*\*c\*\*-\*\*RET\*\*; ANP-A=Atrial natriuretic peptide receptor-A;\*\*

\*\*ANP-B=Atrial natriuretic peptide receptor-B; MOS=c-mos; PBS2=polyxyn B\*\*

\*\*antibiotic resistance gene product; STE7=sterile mutant wild-type allele\*\*

\*\*gene. . . .\*\*

\*\*. . .

\*\*13. 5,629,302, May 13, 1997, Biotenside esters and phosphatides with\*\*

\*\*vitamin-D and vitamin-E compounds; processes for their preparation;\*\*

\*\*spontaneously dispersible agents containing these

compounds, and their\*\*

\*\*use for the treatment of tumors; Carl Eugster, et al., 514/167; 552/653\*\*

\*\*[IMAGE AVAILABLE]\*\*

\*\*. . .

\*\*US PAT NO: 5,629,302 [IMAGE AVAILABLE]

L8: 13 of 24\*\*

\*\*. . .

\*\*DETDESC: \*\*

\*\*. . .

\*\*DETD(98)\*\*

\*\*. . . .\*\*

\*\*1016 cm.sup.-1 nu.(C.dbd.O) \*\*

\*\* 970 cm.sup.-1 trans C.dbd.C\*\*

\*\* .delta.(CH)\*\*

\*\* NIR 1627 cm.sup.-1 (C.dbd.C) [D.sub.3]\*\*

\*\* 1583 cm.sup.-1 (C.dbd."C") [\*Ret\*\*.]\*\*

\*\*DL-alpha-Tocopherol-all trans-retinate\*\*

\*\* RI 1.55350\*\*

\*\* NIR 1583 cm.sup.-1 (C.dbd."C")

\*\* [\*Ret\*\*.]\*\*

\*\*Ergocalciferol-13 cis-retinate\*\*

\*\* NIR 1627 cm.sup.-1 (C.dbd.C) [D.sub.2]\*\*

\*\* 1585 cm.sup.-1 (C.dbd."C") [\*Ret\*\*.]\*\*

\*\* Cholecalciferol-13 cis-retinate\*\*

\*\* NIR 1627 cm.sup.-1 (C.dbd.C) [D.sub.3]\*\*

\*\* 1583 cm.sup.-1 (C.dbd."C") [\*Ret\*\*.]\*\*

\*\* DL-alpha-Tocopherol-13 cis-retinate\*\*

\*\* NIR 1583 cm.sup.-1 (C.dbd."C")

\*\* [\*Ret\*\*.]\*\*

\*\*. . . .\*\*

\*\* N.B.:\*\*

\*\* RI = Refraction Index, measured on a DUR Refractometer

\*\* Schmidt, \*\*

\*\* Haensch, \*\*

\*\* Berlin, \*\*

\*\* IR, . . . \*\*

\*\*. . .

\*\*14. 5,514,546, May 7, 1996, Stem-loop oligonucleotides

containing\*\*  
\*\*parallel and antiparallel binding domains; Eric T. Kool,  
435/6; 535/23.1, \*\*  
\*\*24.3 [IMAGE AVAILABLE]\*\*

\*\*\*  
\*\*US PAT NO: 5,514,546 [IMAGE AVAILABLE]  
L8: 14 of 24\*\*

\*\*\*  
\*\*DETDESC: \*\*

\*\*\*  
\*\*DETD(112)\*\*

\*\*\* Moreover, . . . c-ets, c-fgf, c-fms, c-fos, c-has/bas, her-2  
neu, \*\*  
\*\*c-int, c-jun, c-kit, c-mas, c-met, c-mos, c-myb, c-myc,  
N-myc, p53, ras, \*\*  
\*\*c-Ha-ras, c-rel, \*\*c-\*\*ret\*\*, c-ros, c-sec, c-sis, c-ski,  
c-snoA, \*\*  
\*\*c-snoN, c-spi, c-src, c-syn, c-trk, c-vav and c-yes.\*\*

\*\* 15. 5,502,224, Mar. 26, 1996, Biotenside esters and  
phosphatides with\*\*  
\*\*vitamin-D and vitamin-E compounds; Carl Eugster, et al.,  
552/653 [IMAGE]\*\*  
\*\*AVAILABLE]\*\*

\*\*\*  
\*\*US PAT NO: 5,502,224 [IMAGE AVAILABLE]  
L8: 15 of 24\*\*

\*\*\*  
\*\*SUMMARY: \*\*

\*\*\*  
\*\*BSUM(123)\*\*

\*\*\* 1016 cm.sup.-1 nu.(C.dbd.O) \*\*  
\*\* 970 cm.sup.-1 trans C.dbd.C\*\*  
\*\* .delta.(CH)\*\*  
\*\* NIR 1627 cm.sup.-1 (C.dbd.C) [D.sub.3 ]\*\*  
\*\* 1583 cm.sup.-1 (C.dbd.\*\*C\*\*) [\*\*Ret\*\*.].\*\*

\*\*DL-alpha-Tocopherol-all trans-\*\*

\*\* RI 1.55350\*\*

\*\*retinol NIR 1583 cm.sup.-1 (C.dbd.\*\*C\*\*)

[\*\*Ret\*\*.]\*\*

\*\*Ergocaliferol-13 cis-retinol\*\*

\*\* NIR 1627 cm.sup.-1 (C.dbd.C) [D.sub.2.2 ]\*\*  
\*\* 1583 cm.sup.-1 (C.dbd.\*\*C\*\*) [\*\*Ret\*\*.].\*\*

\*\*Cholecalciferol-13 cis-retinol\*\*

\*\* NIR 1627 cm.sup.-1 (C.dbd.C) [D.sub.3 ]\*\*  
\*\* 1583 cm.sup.-1 (C.dbd.\*\*C\*\*) [\*\*Ret\*\*.].\*\*

\*\*DL-alpha-Tocopherol-13 cis-\*\*

\*\* NIR 1583 cm.sup.-1 (C.dbd.\*\*C\*\*)

[\*\*Ret\*\*.]\*\*

\*\*retinol\*\*

\*\*\*  
\*\*\*) N.B.: RI = Refraction Index, measured on a DUR

Refractometer Schmidt +\*\*

\*\* Haensch, Berlin.\*\*

\*\* IR. . . \*\*

\*\*\*

\*\* 16. 5,466,596, Nov. 14, 1995, Tissue specific transcriptional  
regulatory\*\*

\*\*element, Martin L. Breitman, et al., 435/354, 69.1, 70.3;  
536/24.1 [IMAGE]\*\*  
\*\*AVAILABLE]\*\*

\*\*\*  
\*\*US PAT NO: 5,466,596 [IMAGE AVAILABLE]

L8: 16 of 24\*\*

\*\*\*  
\*\*DETDESC: \*\*

\*\*\*  
\*\*DETD(58)\*\*

\*\*\*

\*\* Comparison . . . Maniatis, T. (1989). Molecular Cloning.  
Cold Spring\*\*

\*\*Harbor Laboratory Press) and 45% to the transmembrane  
RTK encoded by the\*\*

\*\*human \*\*c-\*\*ret\*\* protooncogene (Takahashi &  
Cooper, 1987). In\*\*

\*\*addition, striking sequence identity is observed to a 65  
amino acids\*\*

\*\*residue sequence encoded. . . \*\*

\*\*\*  
\*\* 17. 5,340,853, Aug. 23, 1994, Polymer-based swelling and  
absorbing\*\*

\*\*agents with an improved degradability and an improved  
absorption for\*\*

\*\*water, aqueous solutions and body liquids and the use of  
said agents for\*\*

\*\*the production of hygienic articles and for soil conditioning;  
Miroslav\*\*

\*\*Chmelir, et al., 524/56, 54, 55; 525/54.23, 54.31, 54.32;  
604/368, 372\*\*

\*\*[IMAGE AVAILABLE]\*\*

\*\*\*  
\*\*US PAT NO: 5,340,853 [IMAGE AVAILABLE]

L8: 17 of 24\*\*

\*\*\*  
\*\*DETDESC: \*\*

\*\*\*  
\*\*DETD(10)\*\*  
\*\* . . . \*\*  
\*\*0.50 \*\*  
\*\*Ex. 9: 33 67 0.50\*\*

\*\*\* Determination of the DAT-values\*\*

\*\* Max.sup.(a)\*\*  
\*\* Ret.sup.(a)\*\*  
\*\* Max.sup.(b)\*\*  
\*\* Ret.sup.(b)\*\*  
\*\* Max.sup.(\*\*c\*\*)\*\*  
\*\* "Ret\*\*.sup.(c)\*\*  
\*\* (ml/g) (ml/g) \*\*  
\*\* (ml/g) (ml/g) \*\*  
\*\* (ml/g) \*\*

\*\* 50.3 26.9 50.3 26.9 50.3 26.9\*\*

\*\* 6.1 4.8 . . . \*\*

\*\*DETDESC: \*\*

\*\*\*  
\*\*DETD(13)\*\*

\*\* . . . \*\*  
\*\*0.60 \*\*  
\*\*Ex. 13: 67 33 0.75\*\*

\*\*\* Determination of the DAT-values\*\*

\*\* Max.sup.(a)\*\*  
\*\* Ret.sup.(a)\*\*  
\*\* Max.sup.(b)\*\*  
\*\* Ret.sup.(b)\*\*  
\*\* Max.sup.(\*\*c\*\*)\*\*  
\*\* "Ret\*\*.sup.(c)\*\*  
\*\* (ml/g) (ml/g) \*\*  
\*\* (ml/g) (ml/g) \*\*  
\*\* (ml/g) \*\*

\*\* 49.8 26.5 49.8 26.5 49.8 26.5\*\*

\*\* 5.5 2.2 . . . \*\*

\*\* 18. 5,202,403, Apr. 13, 1993, Lignin modified

phenol-formaldehyde\*\*

\*\*resins; Glen A. Doering, 527/403; 525/54.42; 528/155;  
530/501, 502 [IMAGE]\*\*

\*\*AVAILABLE]\*\*

\*\*\*  
\*\*US PAT NO: 5,202,403 [IMAGE AVAILABLE]

L8: 18 of 24\*\*

\*\*\*  
\*\*DETDESC: \*\*

\*\*\*  
\*\*DETD(39)\*\*

\*\* . . . \*\*

\*\*VI \*\*

\*\*\*  
\*\* 2 hr. Boil Internal Bond (avg.)\*\*  
\*\* 24-hr. Water Soak\*\*

\*\* Mat BIB.sup.1 (avg.)\*\*

\*\* Mois\*\*

\*\* DENg (kg/\*\*c\*\*\*\*

\*\* "RET\*\*.sup.2\*\*

\*\* BTS.sup.3\*\*

\*\* DEN TS.sup.4\*\*

\*\* WA.sup.5\*\*

\*\*Sample\*\*

\*\* (%) /cm.sup.3\*\*

\*\* m.sup.2\*\*

\*\* (%) (%) g/cm.sup.3\*\*

\*\* (%) \*\*

\*\*\*  
\*\* 19. 5,028,397, Jul. 2, 1991, Catalytic converter; Richard P.

Merry, \*\*

\*\*422/179; 60/299, 301; 422/180, 221, 222; 423/625, 628;

501/95.1, 133,\*\*

\*\*153, 154; 502/263, 407, 415 [IMAGE AVAILABLE]\*\*

\*\*\*  
\*\*US PAT NO: 5,028,397 [IMAGE AVAILABLE]

L8: 19 of 24\*\*

\*\*\*  
\*\*DETDESC: \*\*

\*\*\*  
\*\*DETD(9)\*\*

\*\*\*  
\*\*TABLE I\*\*

\*\*\*  
\*\* Pressure (kPa) Exerted at\*\*

\*\* Various Temperatures\*\*

\*\* R.T/ 800.degree. C\*\* /\*\*

\*\* "Ret\*\*. to/\*\*

\*\* Mount R.T. @ 530.degree. C. @\*\*

\*\* R.T. @\*\*

\*\* Density 4.24 mm 3.99 mm 4.24 mm\*\*

\*\*Mounting . . . \*\*

\*\*\*  
\*\* 20. 4,929,429, May 29, 1990, Catalytic converter; Richard P.  
Merry, \*\*

\*\*422/179, 221 [IMAGE AVAILABLE]\*\*

\*\*\*  
\*\*US PAT NO: 4,929,429 [IMAGE AVAILABLE]  
L8: 20 of 24\*\*

\*\*\*  
\*\*DETDESC: \*\*

\*\*\*  
\*\*DETD(9)\*\*

\*\*\*  
\*\* TABLE I\*\*

\*\*\*  
\*\* Pressure (kPa) Exerted at Various  
Temperatures\*\*  
\*\* Mount Density\*\*  
\*\* R.T/R.T. @\*\*  
\*\* 800.degree. C/530.degree. C\*\*  
\*\*C\*\*.\*\*  
\*\* "Ret\*\*. to/R.T. @\*\*

\*\*Mounting Mats (g/cm.sup.3)\*\*  
\*\* 4.24 mm gap\*\*  
\*\* 3.99 mm gap\*\*  
\*\* 4.24 mm\*\*

\*\*\*  
\*\* Ceramic Fiber/Intumescent. . . \*\*

\*\*\*  
\*\* 21. 4,692,147, Sep. 8, 1987, Drug administration device;  
Stephen R.\*\*

\*\*Duggan, 604/93; 128/DIG.12; 604/891.1 [IMAGE  
AVAILABLE]\*\*

\*\*SYSTEM LIMITS EXCEEDED - DISPLAY ENDED\*\*  
\*\*YOU HAVE RECEIVED THIS ERROR MESSAGE 2  
CONSECUTIVE TIMES\*\*

\*\*The patent you are attempting to display contains a  
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HIT\*\*

\*\*format or any other display format instead of KWIC. (Enter  
HELP\*\*

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been \*\*

\*\*attempting a character string search in Display Browse, end  
Display \*\*

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Search command. \*\*

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